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Acute kidney injury in neonatal intensive care unit and the significance of nRIFLE criteria on diagnosis and prognosis

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ABSTRACT

Objectives: The objective of this study is to identify factors that affect the severity of acute kidney injury (AKI) using neonatal RIFLE (Risk, Injury, Failure, Loss of function, End-stage kidney disease) criteria; to identify the impact of these criteria and the factors on mortality rates and to determine the one-year clinical outcome.

Methods: Five hundred and thirty-two inpatients who were admitted to Gazi University, Faculty of Medicine, Neonatal Intensive Care Unit (NICU) between 2006 and 2016 have been examined retrospectively.

Results: Acute kidney injury developed in the first month of life in 85 (16%) patients. Thirty-nine (7.35%) of the cases were term and 46 (8.65%) were preterm. Among these patients, 33 (38.8%) were in the risk group, 18 (21%) in the injury group, and 34 (40%) in the failure group. Metabolic acidosis and edema were the most commonly seen findings as acute kidney injury scores increased. According to the neonatal RIFLE (nRIFLE) criteria, the severity of AKI was significantly correlated ($P<0.05$) with metabolic acidosis (71%) and edema (50.5%). There was a positive correlation between urinary output and pH, bicarbonate, glomerular filtration rate, and sodium values in patients with AKI, while a negative correlation between urinary output and BUN, creatinine, potassium, phosphorus, and uric acid was found. Regarding the nRIFLE criteria, the frequency of hyponatremia and hyperpotassemia was increased as the AKI severity score was increasing ($P<0.05$). The mortality rate was 54% in the newborn period and factors that significantly affect mortality were the need for mechanical ventilation, sepsis, nephrotoxicity, and acidosis ($P<0.05$).

Conclusions: The nRIFLE criteria based on urinary output is a guide for clinicians to diagnose AKI. There is a need to work on new markers in future studies.

Keywords: Acute kidney injury, risk factors, nRIFLE, newborn

Acute kidney injury (AKI) is a sudden renal dysfunction resulting from changes in extracellular fluid volume, fluid electrolyte and acid-base balance, and insufficiency in nitrogen excretion. It is a complex disease with many causes, pathophysiological pathways, and clinical importance [1].

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It peaks in neonatal intensive care unit (NICU) patients and especially affects premature. The incidence of renal failure in newborns ranges from 6% to 24% in the NICU. Clinical manifestations of acute kidney injury range from minimal renal failure to requiring renal replacement therapy [2]. Exposure to perinatal events such as nephrotoxic drugs, sepsis, and asphyxia in the neonatal period carries a great risk for the development of acute kidney injury. Current studies indicate that there is a relationship between morbidity and mortality and acute kidney injury in these patients. Close monitoring of patients at risk and early recognition of changes in kidney function are the keys to improving the process [3].

Due to the use of diverse definitions for AKI and the lack of a standard definition in clinical trials in newborns, the incidence and mortality rates of AKI vary widely. The serum creatinine value is a restricted laboratory parameter in the definition of AKI. Therefore, neonatal RIFLE (Risk, Injury, Failure, Loss of function, End-stage kidney disease) criteria were developed based on urine output (UO). It has been notified that a better classification will be made at this point and diuresis can be used as an alternative method for defining high-risk NICU patients [4, 5].

Our study aimed to determine the risk factors affecting the severity of AKI and to establish the effect of these risk factors on newborn mortality rates by using the neonatal RIFLE (nRIFLE) criteria in newborns. Another aim of the study was to monitor the renal functions of newborns who lived at least one year during follow-up.

METHODS

The outcomes of 532 patients who were admitted to NICU between 2006 and 2016 have been examined retrospectively and 85 newborns diagnosed with AKI were enrolled into the study. The diagnosis of neonatal AKI was based on decreased urine output, taking into account gestational and postnatal age. Urine output was systematically measured by diaper weight or neonates were catheterized. The Ethical Committee for Medical Research of Gazi University approved this study under protocol number 19026.

Classification of AKI severity was done according to the nRIFLE criteria used by Bezerra and his colleagues in 2013. “Risk” was defined as UO<1.5 ml/kg/h in 24 hours, ‘’injury’’ was defined as UO<1 ml/kg/h in 24 hours, and ‘’failure’’ was defined as UO <0.7 ml/kg/h in 24 hours or anuria for 12 hours. “Loss” defined as renal failure>4 weeks and “end-stage renal disease” defined as renal failure>3 months were not used in our study [4, 5].

Patients included in this study were assessed in terms of risk factors that affect AKI severity and mortality.

Blood Urea Nitrogen (BUN), serum creatinine, uric acid, sodium (Na), potassium (K), phosphorus (P), urinalysis, blood gas and blood culture tests were recorded at the time of admission. Electrolyte changes and the presence of acidosis were noted. pH<7.35 with serum bicarbonate<21 mmol/L in blood gas was evaluated as acidosis.

Normal ranges for blood Na, K and Ca levels were accepted as 135-145 mEq/L; 3.5-5.5 mEq/L and 8.5-10.5 mg/dL, respectively.

Microorganisms were grown in the blood and urine cultures of septic patients, antibiotics were administered and anomalies in the abdominal ultrasonography of the patients were recorded. Vancomycin, amikacin, amphotericin B, meropenem, and gentamicin were agreed as nephrotoxic antibiotics (Vancomycin, amikacin, amphotericin B, meropenem and gentamicin were considered nephrotoxic antibiotics.).

Oliguria, hyperuricemia, hyperpotassemia, hypervolemia, and metabolic acidosis were defined as indications for peritoneal dialysis treatment.

The patients older than 28 postnatal days when AKI was diagnosed, patients with <24 hours NICU stay and the 22 newborns without adequately obtainable data were excluded from the study.

Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS) 21.0 was used for statistical analysis. To examine the impact of the independent variables in the sample group, nonparametric analysis methods were used for the groups composed of less than 30 people whereas parametric analysis methods were used for the group of more than 30 people.

Descriptive analysis methods were used for the sociodemographic data of the sample group. Chi-Square, Kruskal-Wallis analysis, and Mann Whitney U were used to determine whether there is any difference in

the independent variables among the three groups that constitute the sample group. The Spearman correlation method was used to examine the relationship between the independent variables.

RESULTS

Of the 85 newborns evaluated according to the nRIFLE criteria, 33 were in the risk group, 18 in the injury group, and 34 in the failure group, respectively.

Demographic information of the patients was examined. According to the severity of AKI, it was identified that there was no significant difference among groups in terms of gender, gestational age, birth weight, and period of hospitalization. The mean age at diagnosis of AKI was 5.96±6.14 days. The mean and standard derivation (SD) of birth weight of newborns diagnosed as AKI were 2162±1069 g and gestational ages were 33.95±5.52 weeks.

The incidence of metabolic acidosis was 71% and the frequency of edema was 50.5% in newborns diagnosed with AKI. The incidence of acidosis and edema was higher in the failure group (P<0.05) (Table 1).

The relationship between the duration of mechanical ventilation and urine output was assessed and no

Table 1. Comparison of risk factors in the groups

Risk Factors	Risk UO<1.5 mL/ kg/h for 24 h		Injury UO<1.0 mL/ kg/h for 24 h		Failure UO<0.7 mL/ kg/h for 24 h or anuric for 12 h		Total		P value
	n	%	n	%	n	%	n	%	
Acidosis	19	31.7	13	21.7	28	46.7	60	100	**0.049**
Edema	4	9.3	10	23.3	29	67.4	43	100	**<0.001**
Mechanic ventilation	24	34.8	15	21.7	30	43.5	69	100	0.259
Nephrotoxic agent use	29	37.2	16	20.5	33	42.3	78	100	0.347
Surgical intervention	10	27	9	24.3	18	48.6	37	100	0.144
Septicemia	29	37.2	15	19.2	34	43.6	78	100	0.067
Respiratory system problems	19	35.8	13	24.5	21	39.6	53	100	0.691
Congenital heart disease	28	41.8	14	20.9	25	37.3	67	100	0.522
Asphyxia/ hypoxia	7	33.3	3	14.3	11	52.4	21	100	0.385
Congenital urinary anomalies	10	40	2	8	13	52	25	100	0.123
Gastrointestinal tract problems	14	43.8	7	21.9	11	34.4	32	100	0.691
Inotrope requirement	19	31.7	15	25	26	43.3	60	100	0.097
Urinary tract infection	2	28.6	0	0	5	71.4	7	100	0.157
Phototherapy	17	48.6	6	17.1	12	34.3	35	100	0.301
Intracranial hemorrhage	11	57.9	3	15.8	5	26.3	19	100	0.152
Mother's health problems	18	38.3	9	19.1	20	42.6	47	100	0.826
Mother's medicine use	12	41.4	5	17.2	12	41.4	29	100	0.880

UO = urine output

Table 2. Laboratory Findings Based on the Classification of Acute Kidney Injury Severity

Laboratory Findings	Risk UO<1.5 mL/kg/h for 24 h			Injury UO<1.0 mL/kg/h for 24 h			Failure UO<0.7 mL/kg/h for 24 h or anuric for 12 h			Total			P value
	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD	
pH	32	7.32	0.1	18	7.29	0.14	33	7.24	0.13	83	7.28	0.13	**0.033**
HCO3 (mmol/L)	32	19.7	3.8	18	18.74	4.68	33	17.5	5.13	83	18.62	4.61	0.085
PCO2 (mm Hg)	32	38.78	10.54	18	38.88	10.71	33	41.51	12.37	83	39.89	11.28	0.602
GFR (mL/min)	7	15.35	6.70	7	15.13	8.31	22	9.72	4.63	36	11.86	6.32	**0.047**
BUN (mg/dL)	33	21.02	13.82	18	33.56	27.78	34	32.72	22.47	85	28.36	21.49	**0.037**
Creatinine (mg/dL)	33	0.89	0.47	18	1.13	0.75	34	2.01	1.28	85	1.39	1.05	**<0.001**
Uric acid (mg/dL)	33	4.92	3.65	18	6.68	4.21	34	8.65	3.98	85	6.79	4.2	**<0.001**
Sodium (mmol/L)	33	140.45	6.66	18	135.78	7.94	34	134.18	8.17	85	136.95	8	**0.003**
Potassium (mEq/L)	33	4.28	0.85	18	5.13	1.67	34	5.27	1.51	85	4.86	1.4	**0.006**
Calcium (mg/dl)	33	8.89	0.82	18	8.36	1.36	34	8.34	1.14	85	8.56	1.1	0.063
Phosphorus (mg/dL)	33	4.63	1.69	16	5.48	1.89	34	5.63	1.94	85	5.2	1.87	**0.038**
Albumin (g/dL)	32	2.74	.0.54	18	2.71	0.76	31	2.66	0.65	81	2.7	0.63	0.794

BUN = blood urea nitrogen, GFR = glomerular filtration rate, SD = standard deviation, UO = urine output

significant relationship was found (r=0.196, P=0.08). There was no notable difference between groups according to nRIFLE criteria in terms of mechanical ventilation time (P=0.164). The failure group had significantly lower pH, glomerular filtration rate (GFR), and serum sodium values than the risk group. Serum BUN, creatinine, uric acid, potassium, and phosphorus values were significantly higher in the failure group (Table 2). The relationship between laboratory results and the urine output of the study group was shown in Table 3. A significant positive correlation between urinary output and pH (r=0.308, P<0.01), HCO3 (r=0.227, p<0.05), GFR (r=0.372, P<0.05), serum sodium (r=0.357, P<0.01) when the table was observed. A significant negative correlation between urinary output and BUN (r=-0.253, P<0.05), creatinine (r=-0.493, P<0.01), uric acid (r=-0.44, P<0.01), serum potassium (r=-0.33, P<0.01), serum phosphorus (r=-0.248, P<0.05). No important relationship was found between urinary output and the other values (P>0.05) (Table 3).

A significant difference in the albumin values of the edematous and non-edematous patients was found. Eventually, it was observed that there was a difference in albumin values between groups (P<0.05). Patients with edema (mean albumin = 2.56±0.63 g) had significantly lower albumin values than those without edema (mean albumin = 2.85±0.60 g).

According to AKI severity, the distribution of hyponatremia, hypernatremia, and hyperpotassemia was found statistically significant (P<0.05). The majority of patients with hyponatremia and hyperpotassemia were found in the failure group.

Forty-six infants with AKI died in the neonatal period. According to the nRIFLE, no relationship was found between the AKI severity and the increase in

Table 3. Correlation between laboratory values and urine outflow of the all infants

Laboratory Values	Urine Outflow	
	R	P value
pH	0.308	**0.006**
HCO3 (mmol/L)	0.227	**0.044**
PCO2 (mm Hg)	-0.116	0.310
GFR (mL/min)	0.372	**0.036**
BUN (mg/dL)	-0.253	**0.023**
Creatinin (mg/dL)	-0.493	**0.000**
Uric acid (mg/dL)	-0.440	**0.000**
Sodium (mmol/L)	0.357	**0.001**
Potassium (mmol/L)	-0.330	**0.003**
Calcium (mg/dL)	0.180	0.107
Phosphorus (mg/dL)	-0.248	**0.027**
Albumin (g/dL)	0.081	0.483

BUN = blood urea nitrogen, GFR = glomerular filtration rate

mortality rate (P=0.437).

A statistically significant relationship between mechanical ventilation (P<0.001), acidosis (P<0.01), sepsis (P<0.05), and nephrotoxicity (P<0.05) with mortality rate was found (Table 4). The phi values of variables with a significant difference were calculated. Mechanical ventilation (Ø=0.46) had a greater effect on mortality rate than metabolic acidosis (Ø=0.32), sepsis (Ø=0.32), or nephrotoxicity (Ø=0.24).

Most of the patients were followed by local healthcare centers, so the regular follow-up of all the patients in our study in terms of kidney function could not be done. Only 15 of the 36 patients who survived were examined regularly in the pediatric nephrology department. Renal function loss was detected by imaging methods in five patients. An increase in renal parenchymal echogenicity was observed by ultrasonography in three patients. Three patients were followed up with a diagnosis of hydronephrosis. Antihypertensive treatment was started in seven patients during the follow-up. Renal artery stenosis was diagnosed by Doppler ultrasonography in two of seven patients. The mean follow-up period was 20.13 ± 18.68 months and no patient developed chronic kidney failure in this period. However, it is known that our patients have been at risk for late sequelae, especially the patients with renal scintigraphic changes and renal dysfunction should be followed closely.

DISCUSSION

Acute kidney injury is a complicated clinical condition with a sudden decrease in kidney function and a serious problem in terms of morbidity and mortality in newborns. Serum creatinine level and urine output are frequently used in the diagnosis of AKI in newborns. However, there is no consensus on these criteria in the literature and there are different AKI definitions. In 2013, Bezerra and colleagues created the nRIFLE criteria reason that newborns have their physiopathology. In line with the nRIFLE criteria, if oliguria is accepted below 1.5 mL/kg / h, it is stated that risk factors and complications for AKI might increase. It was reported that a better classification would be made on this scale and diuresis could be used as an appropriate alterna-

Table 4. Factors Affecting Mortality Rate in Neonates with Acute Kidney Injury

Parameters	Patients Decreased		Patients Living		Total		P
	N	%	N	%	N	%	
Mechanical ventilation	45	65.2	24	34.8	69	100	**0.000**
Metabolic acidosis	39	65	21	35	60	100	**0.004**
Septicemia	45	57.7	33	42.3	78	100	**0.044**
Dialysis	14	66.7	7	33.3	21	100	0.184
Asphyxia/Hypoxia	15	71.4	6	28.6	21	100	0.067
Surgical intervention	24	64.9	13	35.1	37	100	0.081
Nephrotoxicity	45	57.7	33	42.3	78	100	**0.044**

tive method for defining high-risk NICU patients [4, 5]. The most important reason for this is that the serum creatinine value used in the AKI definition is limiting. The serum creatinine level of the infants reflects the creatinine level of the mother in the early postnatal period. In addition, the decrease in serum creatinine level may last days or weeks depending on gestational age. Especially, premature infants may have a higher serum creatinine level than their mothers. Serum creatinine ultimately does not change until renal function decreases by 25-50% and begins to increase after 24-48 hours from the onset of injury [3, 6, 7].

Complexity in the evaluation of renal physiology and serum creatinine level makes AKI staging difficult. Due to the disadvantages of using serum creatinine levels, recent studies have focused on new markers [8]. nRIFLE criteria were used for the diagnosis of AKI in our study because our study was retrospective, the use of new markers in the diagnosis of AKI was not possible, and achieving serum creatinine values was difficult.

In our study, there was no significant relationship between the distribution of demographic data of newborns with AKI and AKI severity scores. It is stated in the literature that acute renal injury in the neonatal period is usually associated with low gestational weeks and low birth weight in preterm infants [9]. But similar to our study, Cataldi *et al*. [10] found no correlation between low birth weight, low age of gestation, and acute renal injury. This is explained by the difficulty of making comparisons because of the differences in the population and the criteria used to calculate renal function.

Need for mechanical ventilation, the occurrence of sepsis, hypervolemia, metabolic acidosis, and asphyxia was identified as independent risk factors for the development of AKI in the literature [2, 9, 11, 12]. In our study, only metabolic acidosis and hypervolemia were found as risk factors among these factors which significantly increase AKI severity ($P<0.05$). Like our study, Askenazi *et al*. [13] had also shown that hypervolemia was a risk factor for AKI and increased the mortality rate.

Mathur *et al*. [14] stated that sepsis may cause renal failure through shock, hemorrhage, and heart failure. In our research, it was found that sepsis had an important effect on the increase in the severity of AKI, although it was not statistically significant ($P=0.067$). This finding may result from our patient population, the majority of them were severely ill.

Cataldi *et al*. [10] showed that 50% of neonates were exposed to at least one nephrotoxic medication. It was frequently mentioned that non-steroidal anti-inflammatory drugs (NSAIDs) are used for patent ductus arteriosus (PDA) occlusion, and diuretics for fluid electrolyte treatment [10]. There was no substantial relationship between AKI severity and nephrotoxic drug use in our research. This condition can be explained by the adjustment of nephrotoxic drug doses according to the kidney function to prevent any toxic effect on kidney function.

In the study of Bolat *et al*. [15], maternal illness and medication use in pregnancy were described as risk factors affecting AKI. Taking antibiotics during pregnancy is known to affect the renal function of the newborn and antenatal steroids cause low birth weight and worsen organogenesis. In our study, it was observed that the maternal illness rate of neonates with AKI was 55% and the rate of medication use in pregnancy was 34%. As opposed to this result, no significant relationship was found between maternal illness ($P=0.826$) and maternal drug use ($P=0.88$) with increasing AKI severity in our study. Our small sample size may affect this result.

In the literature, the mortality of patients with AKI has ranged from 25% to 78% [4, 5]. In this study, the mortality rate in the group of newborns with AKI was high (54%). Our high mortality rate can be explained by the fact that our clinic is a tertiary center and complicated patients have been referred to us frequently.

In our study, it was observed that metabolic acidosis, sepsis, mechanical ventilation, and nephrotoxicity were significantly associated with the mortality of newborns. We also found that the need for mechanical ventilation was more effective on mortality compared to having metabolic acidosis, sepsis, and nephrotoxicity. In line with our results, Koralkar *et al*. found that the need for mechanical ventilation in AKI increased the mortality rate nine times [16].

In the study of Mathur *et al*. [14], it was found that sepsis was associated with an increased risk of AKI, so most of the patients with sepsis were lost. The mortality rate in infants with sepsis in our study was 57.7%.

There have been some studies in the literature on the long-term prognosis of AKI in newborns. These

studies describe the possibility of long-term injury and emphasize that hypertension, chronic kidney disease (CKD), and renal concentration defects may develop. They also emphasized the importance of long-term follow-up in newborn babies.

In the study of Moghal *et al*. [17], it was emphasized that serum creatinine, blood pressure, urinalysis, and albumin/creatinine ratio should be evaluated, and possible abnormalities should be followed up in the long term. Abitbol *et al*. [18] studied 20 very low birth weight infants and found proteinuria, increased serum creatinine level, and a tendency to obesity as risk factors for AKI.

In our study, 15 patients were followed up for a mean of 20.13±18.68 months. It was found that the renal functions of 5 of 15 patients were decreased in the imaging methods and close follow-up should be suggested.

Limitations

First, it was retrospective, and we couldn't find all the information we needed. Second, it was a single-center study, so the size of the patient population was small. Third, the diagnostic criteria of AKI couldn't be compared with the others.

CONCLUSION

Neonatologists and pediatric nephrologists must work together to reduce the morbidity and mortality of AKI in neonates and to obtain better results in these patients. The rifle criteria can be a guideline for the diagnosis of AKI for clinicians, but they need to be enhanced. Moreover, novel biomarkers to predict AKI severity should be defined. Further studies to identify the long-term outcomes of AKI and the risk of CKD are needed.

Authors' Contribution

Study Conception: ÇC, NB, CT, YA, SABE; Study Design: ÇC, NB, CT, YA, SABE; Supervision: ÇC, NB, CT, YA, SABE; Funding: N/A; Materials: N/A; Data Collection and/or Processing: ÇC, NB, CT, YA, SABE; Statistical Analysis and/or Data Interpretation: ÇC, NB, CT, YA, SABE; Literature Review: ÇC, NB; Manuscript Preparation: ÇC, NB and Critical Review: ÇC, NB, CT, YA, SABE.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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