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Predictive Factors of Acute Renal Failure in the Neonates with Respiratory Distress Syndrome

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ABSTRACT

Background: Preterm birth occurs in a large number of pregnancies, and its incidence has been reported to be on the rise. Acute kidney injury (AKI) is a common complication in the premature infants with respiratory distress syndrome (RDS). The present study aimed to determine the predictive factors, clinical courses, and outcomes of AKI in the neonates with the clinical and radiological manifestations of RDS.

Methods: Medical records of 84 premature neonates with RDS were evaluated in two groups of case (with AKI) (n=34) and control (without AKI) (n=50). Diagnosis of AKI was based on the increased level of serum creatinine (>1.5 mg/dL) after the third day of birth or increasing serum creatinine level. In addition, blood pressure and laboratory findings, including complete blood count, serum electrolytes, and urine volume, were compared between the two groups.

Results: Mean age of the infants with AKI was 5.41±3.29 days, and the majority of the patients had nonoliguric renal failure. Among the samples, 23.5% died, and 76.5% were discharged without renal impairment. Birth weight, systolic blood pressure, blood urea nitrogen, calcium, and pH on admission had significant correlations with the presence of AKI. Moreover, birth weight was observed to be a relatively accurate predictive factor for AKI (AUC=0.08; 95% CI=0.68-0.91), with 73.5% sensitivity and 80% specificity.

Conclusion: According to the results, AKI was more common in the low-birth-weight infants with severe RDS compared to the other subjects.

Keywords: Acute kidney injury, Creatinine, Kidney, Neonates, RDS

Introduction

Despite the remarkable advancement in perinatal and maternal care, the frequency of preterm delivery remains high and seems to be on the rise. Respiratory distress syndrome (RDS) is one of the most common complications of preterm labor (1), which occurs in approximately 50% of very-low-birth-weight infants. Furthermore, RDS is an important cause of prerenal azotemia in premature neonates, with the incidence rate of 25-65% (2).

Immature tubular and glomerular function and impaired adaptive mechanisms are considered to be the leading causes of renal dysfunction and acute kidney injury (AKI) in the premature neonates with RDS (2-4).

Prognosis of AKI is often poor and depends on various factors, such as the underlying etiology, early diagnosis, multiple organ failure, mechanical ventilation, and renal replacement therapy (5). The predisposing factors of AKI have been reported in previous studies. However, there are limited findings regarding AKI and the associated risk factors in the neonates with RDS (1, 2).

The present study aimed to identify the risk factors and clinical course of AKI in the neonates with RDS.

Methods

This cross-sectional study was conducted

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on 84 premature neonates with RDS, who were admitted to Ali Asghar Children's Hospital, which is tertiary care center in Tehran, Iran during 2005-2016. Infants were divided into two groups of case (with AKI) (n=34) and control (without AKI) (n=50). The majority of the patients were referred from other hospitals due to moderate-to-severe RDS. Diagnosis of RDS was based on the early clinical manifestations at birth, such as grunting, nasal flaring, intercostal and subcostal retractions, cyanosis associated with diagnostic diffuse, symmetrical reticulo-granular radiological patterns, ground-glass appearance, and air bronchogram, and response to surfactant treatment, excluding the other causes of RDS (6). In addition, diagnosis of AKI was based on the presence of one or more of the following criteria: serum creatinine (Cr) of >1.5 mg/dL after the first 48-72 hours of birth with normal maternal serum Cr, doubling serum Cr during admission or increased serum Cr (rate: 0.3 mg/dL/24h).

The study protocol was approved by the localized review board. The primary outcome was death or survival with normal or impaired renal function. Exclusion criteria of the study were as follows: 1) severe perinatal asphyxia; 2) maternal history of renal dysfunction; 3) major congenital anomalies; 4) congenital anomalies of the kidney and urinary tract; 5) genetic syndromes; 6) culture proven septicemia and 7) postoperative AKI.

Medical records of all the neonates were reviewed to extract the demographics characteristics and laboratory findings, including gestational age, gender, birth weight, duration of AKI, mode of delivery, one- and five-minute Apgar scores, premature rupture of membranes (PROM), prenatal drug exposure, intraventricular hemorrhage, pneumothorax, mechanical ventilation, steroid therapy, urine output, surfactant therapy, and initial laboratory tests. Moreover, renal function tests for the blood urea nitrogen (BUN) and Cr levels were performed upon admission, 72 hours later, in the first week of birth, and at discharge. Serum Cr concentration within the first two days of birth was disregarded as it reflected the maternal value.

Measured values of the studied variables were defined, as follows:

Low birth weight; birth weight less of 1,500- 2,500 grams, very low birth weight; birth weight of 1,000-1,500 grams; prematurity: birth at <37 weeks of gestation, confirmed by antenatal ultrasound and Ballard postnatal score; PROM: rupture of membranes at >18 hours before the onset of labor; leukopenia: white blood cells (WBC) of <5,000/mm^3; leukocytosis: WBC of >30,000/mm^3 on the first day of birth and >15,000-20,000/mm^3 on the following days; thrombocytopenia: platelet count of <150,000/m^3; thrombocytosis: platelet count of >400,000/mm3; anemia: hemoglobin level of <14 and 12-13 g/dL in term and very-low-birth-weight infants; metabolic acidosis: serum pH of <7.20 on the first day of birth and <7.35 on the following days; hyponatremia: serum sodium of <133 mmol/L; hyper-natremia: serum sodium of >150 mmol/L; hypokalemia: serum potassium of <3.2 mmol/L in the first week of birth and <3.4 mmol/L from the first week to the first month of birth; hyperkalemia: serum potassium of >5.5 mmol/L in the first week of birth and >6 mmol/L from the first week to the first month of birth; hypocalcemia: serum calcium of <9 mg/dL on the first day, <7 mg/dL on days 1-2, and <9 mg/dL on days 4-7 of birth; azotemia: serum BUN of >25 and >12 mg/dL in preterm and term infants, respectively; oliguria: urine volume of <1 mL/kg/hour after 48 hours of birth.

All the neonates with mild disease received ampicillin and aminoglycoside treatment, and those with severe disease were administered with vancomycin and third-generation cephalosporins. Furthermore, the newborns who were likely to have prerenal dysfunction (oliguria, BUN/Cr>20, and hypovolemia) were subjected to the fluid challenge of 20cc/kg/ normal saline and 5% dextrose water until becoming euvolemic, followed by 2 mg/kg of furosemide infusion in the case of persistent oliguria. Intrinsic renal failure was diagnosed in the patients with intractable oliguria and lack of response to the fluid challenge.

Statistical analysis

Data analysis was performed in SPSS version 22 (Chicago, IL, USA). Normality of the continuous variables was assessed using the Kolmogorov-Smirnov test, and normally distributed continuous variables

were assessed using the independent sample t-test. In addition, Mann-Whitney U test was used for the comparison of the non-normal continuous variables, and Chi-square test was applied to evaluate the qualitative binary data. Also, the Fisher's exact test was used for the 2*2 contingency tables with at least one expected cell of less than five.

All the variables that could predict AKI were assessed using univariate analysis, and the variables with the significance level of ≥0.2 were included in multivariate analysis. Crude and adjusted odds ratio (OR) were obtained by the stepwise backward logistic regression, and the removal probability of less than 0.1 was considered in this regard. Moreover, receiver operating curve (ROC) analysis was used to determine the optimal cutoff point of sensitivity and specificity for the comparison with the "gold standard" in the Stata/SE version 11.

Results

Sample population of the study included 34 infants with AKI, 50% of whom were male, and 50 infants without AKI, 68% of whom were male. Based on the definition of AKI, 24% of the patients had serum Cr of >1.5 mg/dL, 26% had doubling serum Cr during admission, and 50% had increasing serum Cr at the rate of 0.3 mg/dL/24h. Mean age of the neonates with AKI was 5.41±3.29 days, and renal failure was nonoliguric in the majority of the patients (72.5%). In addition, 26.5% of the infants had isolated RDS, and 73.5% were affected by the associated morbidities (e.g., multi-drug administration, birth asphyxia, congenital abnormalities, and infections). Mechanical ventilation was used in 76% of the patients with AKI, 23.5% of whom died, and 76.5% were discharged without residual renal impairment. None of the neonates required renal replacement therapy.

Descriptive analysis of the variables in the two study groups is presented in Table 1. No significant differences were observed between the case and control groups in terms of the age upon admission, gender, PROM, inotrope therapy, mode of delivery, mechanical ventilation, surfactant therapy, and laboratory findings.

Table 2 shows the univariate analysis of the variables (P=0.2), including gender, mechanical ventilation, gestational age, birth weight, serum levels of BUN and calcium, blood pressure, and initial pH, which were also assessed in the multiple backward stepwise regression analysis. Accordingly, birth weight, serum BUN and calcium, blood pressure, and initial pH had significant

Table 1. Demographic Characteristics and Laboratory Findings of Study Groups

Variable	Case (n=34)	Control (n=50)	P-value
Gender (male)	17 (50%)	34 (68%)	0.38
PROM	6 (17.64%)	7 (14%)	0.275
Inotrope Therapy	18 (53%)	10 (20%)	0.06
Mode of Delivery (NVD)	10 (29.4%)	13 (26%)	0.061
Mechanical Ventilation	25 (73.5%)	29 (58%)	0.839
Oliguria	6 (17.64)	0	0.008
Surfactant Therapy	14 (41.18%)	35 (70%)	0.517
GA (week)	29.8±2.7	33.3±3.1	<0.001**
BW (g)	1,405±524	2,068±609	<0.001**
WBC (mm^3)	11,967±6,710	11,598±14,172	0.316
Hgb (g/dL)	13.98±3	13.87±1.9	0.655
Platelet Count (mm^3)	233,029±114,443	232,020±9,2974	0.12
BUN (mg/dL)	20.7±13.3	12.6±6.7	0.001**
Na (meq/L)	138.8±4.8	138.3±4.7	0.826
K (meq/L)	4.6±0.58	4.5±0.64	0.484
Ca (mg/dl)	8.9±0.86	8.6±1.06	0.373
Initial Cr (mg/dl)	0.8±0.32	0.58±0.18	<0.001***
Systolic BP	64.7±10.6	70.2±10.6	0.02**
Serum pH	7.2±0.83	7.33±0.67	0.01**
Duration of Ventilation (day)	8.9±6.2	3.6±2.6	0.007***

*Fisher's exact test; **independent sample t-test; *** Mann-Whitney U test
Values expressed as mean ±SD or number (%)
PROM: premature rupture of membranes; NVD: normal vaginal delivery; GA: gestational age; BW: birth weight; Cr: creatinine; BP: blood pressure

Table 2. Univariate and Multivariate Analysis of Variables Associated with Acute Kidney Injury (AKI)

Variable	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Gender (male)	0.47 (0.19-1.15)	0.1	-	
PROM	0.79 (0.24-2.6)	0.7	-	
Inotrope Therapy	2.8 (0.5-15)	0.24	-	
Mode of Delivery (NVD)	0.8 (0.3-2)	0.6	-	
Duration of Mechanical Ventilation	0.44 (0.17-1.2)	0.1		
Age at Admission	1.03 (0.8-1.3)	0.8	-	
GA	0.68 (0.6-0.8)	<0.001	-	
BW	0.9 (0.9-0.99)	<0.001	0.999 (0.997-1)	0.02
WBC	1	0.8	-	
Hgb	1.02 (0.85-1.2)	0.8	-	
Platelet Count	1	0.9	-	
BUN	1.09 (1.03-1.16)	0.004	1.12 (1.03-1.2)	6×10^{-3}
Na	1.02 (0.93-1.12)	0.6	-	
K	1.2 (0.6-2.5)	0.6	-	
Ca	1.4 (0.9-2.2)	0.15	1.76 (0.88-3.5)	0.1
Systolic BP	0.95 (0.91-0.99)	0.03	0.9 (0.8-0.98)	0.02
Serum pH	3×10^{-4} (5×10^{-7}-0.19)	0.01	7×10^{-6} (1×10^{-10}-0.25)	0.27

Probability for stepwise entry and removal: 0.05 and 0.1, respectively
PROM: premature rupture of membranes; NVD: normal vaginal delivery; GA: gestational age; BW: birth weight; BP: blood pressure

correlations with the presence of AKI.

Sensitivity and specificity of the final variables in the study model and their effective cutoff points in the prediction of AKI are shown in Table 3. Accordingly, birth weight and serum BUN had the highest sensitivity in the prediction of AKI, while birth weight had the highest specificity in the prevention of AKI and was considered the optimal predictive factor for AKI.

Area under the curve (AUC) of each significant variable in comparison with the complete model is presented in Table 4 and Figure 1. According to the results, the AUC of birth weight was 80% (95% CI: 0.68-0.91), which suggested that birth weight was an accurate predictive factor for AKI (P=0.9).

Table 3. Sensitivity, Specificity, and Optimal Cutoff Points

	Sensitivity	Specificity	Cutoff
Complete Model	84	78.3	
Birth Weight	73.5	80	1515
BUN	84.6	51	10.5
Systolic BP	62	60	64.5
Ca	67.6	68.1	8.6
Serum pH	61.7	60	7.29

BUN: blood urea nitrogen; BP: blood pressure

Table 4. AUC for Optimal Cutoff Values of Birth Weight, BUN, Systolic BP, Ca, and First-day pH Compared to Standard Model

	ROC Area	95% CI	P-value
Complete Model (standard)	0.8913	0.81499 0.96762	------
Birth Weight	0.8017	0.68683 0.91664	0.0952
BUN	0.6843	0.55753 0.81117	0.0013
Systolic BP	0.6213	0.48984 0.75277	0.0003
Ca	0.6204	0.47705 0.76382	0.0001
Serum pH	0.6757	0.53385 0.81746	0.0025

BUN: blood urea nitrogen; BP: blood pressure

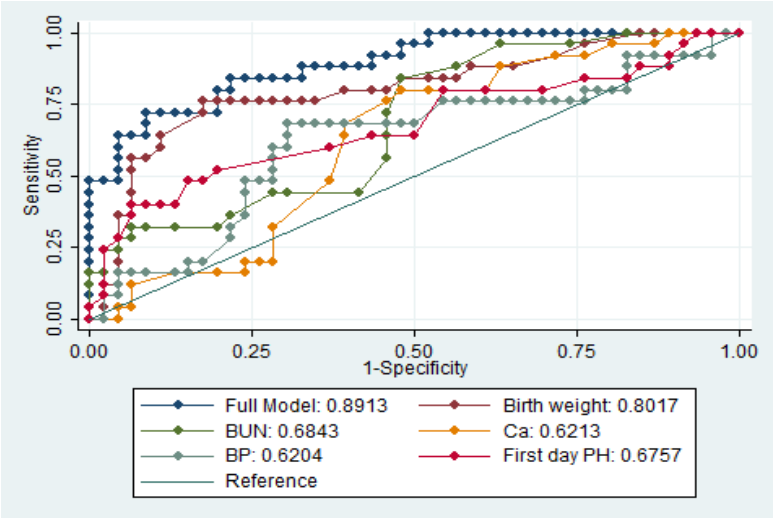

Figure 1. Diagnostic characteristics of BW, BUN, Ca, BP, and serum PH in comparison with full model

Discussion

The present study aimed to identify the predictive risk factors and prognosis of AKI in the neonates with RDS. Several etiologies have been proposed for the increased incidence of renal failure in premature infants, including intrauterine infections, placental insufficiency, maternal drug exposure, hypovolemia, septicemia, drug toxicity, congenital anomalies, low birth weight, prematurity, intubation at birth, RDS, low Apgar scores, and mechanical ventilation (3, 4, 7).

In a study in this regard, Tabel et al. claimed that increased urinary β2-MG levels, sodium fraction excretion, and urinary N-Acetyl-Beta-D glucosaminidase level in the neonates with RDS may indicate hypoxic tubular injury with subclinical proximal and distal tubular dysfunction (1). In the research by Elmas et al., low Apgar scores were observed to be an independent risk factor for AKI in the preterm neonates with RDS (2). Approximately 26% of the patients with AKI in the present study had isolated RDS. However, the majority of thse neonates were also affected by the associated complications, such as multi-drug administration and birth asphyxia. Consistent with our findings, previous studies have denoted no significant differences in the infants with and without AKI in terms of gender, mode of delivery, mechanical ventilation, and surfactant therapy.

Oliguria is considered to be a significant indicator of AKI, which has been reported in 15-90% of the infants with AKI in the previous studies in this regard. However, nonoliguric renal failure has been frequently reported with a favorable prognosis for preserved fluid and electrolyte homeostasis and is associated with a lower mortality rate (2, 8-11). The majority of the patients in the current research had nonoliguric AKI with a lower mortality rate compared to the oliguric group. Since the urine volume of the neonates was not measured before the increase in the serum Cr, it is possible that oliguria was overlooked in the majority of our patients.

Prerenal azotemia is the most common cause of acute renal failure in neonates, with the incidence rate of 85%. Meanwhile, intrinsic and post-renal failures are less frequent, affecting 11% and 3% of these neonates, respectively (8, 12). RDS is a significant cause of prerenal azotemia in infants. The common pathophysiological mechanisms of AKI include the reduction of the renal plasma flow, vasomotor nephropathy aggravated by positive airway ventilation, impaired systemic venous return, and decreased renal blood flow (10, 12). The majority of the patients in the current research had prerenal azotemia, which was responsive to specific medical treatments.

According to the results of the present study, the incidence of AKI was higher in the neonates with low birth weight, low blood pressure, severe acidosis, and low serum calcium compared to the other subjects. Similarly, Cataldi et al. reported the increased severity of RDS to be associated with greater complications and need for intensive treatments in the neonates with AKI (12).

Despite the recent advancement in renal replacement therapy, the mortality rate of neonatal AKI remains high (25-78%) (13). The main causes of AKI mortality are prematurity, multiple organ failure, hypotension, need for vasopressors, mechanical ventilation, and renal replacement therapy, intrinsic failure, use of nephrotoxic drugs, significant acidosis, severe asphyxia, septicemia, congestive heart failure, and oligoanuria (5, 14, 15). In the current research, the mortality rate of AKI was estimated to be 25% among the patients, which was more frequent in the presence of PROM (100%), oligoanuria (94%), inotrope therapy (88%), and mechanical ventilation (88%), as well as in the male infants (70%).

Similarly, our previous study showed increased incidence of AKI in septic neonates with lower birth weight, gestational age, and serum PH in addition to severe sepsis characterized by hypotension, thrombocy-topenia, shock and DIC (16).

The present study had some limitations. Since this was a retrospective study performed based on the medical chart review, we could not include all the required data. As such, it is suggested that large, multicenter prospective studies be conducted for the accurate recognition of the risk factors and independent outcome of AKI in the neonates with RDS.

Conclusion

In conclusion, AKI occurred commonly in neonates with severe RDS. Therefore, rapid diagnosis and improvement of abnormal oxygenation, ventilation, cardiac output, blood pressure, and acidosis are recommended for prevention and effective management of acute renal failure in neonates with RDS.

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Conflicts of interest

None declared.

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