Medeni Med J. 2021;36:193-200
doi:10.5222/MMJ.2021.22687

Original Study

Risk Factors and Outcomes of Acute Kidney Injury in Neonates with Persistent Pulmonary Hypertension of the Newborn

Persistan Pulmoner Hipertansiyonu Olan Yenidoğanlarda Akut Böbrek Hasarı Risk Faktörleri ve Sonuçları

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Ethics Committee Approval: This study was approved by Istanbul Medeniyet University Göztepe Training and Research Hospital Ethics Committee, 26 May 2021, 2021/0288.
Conflict of interest: One of the authors of this article (Fahri Ovali) is an Editorial Board Member of this journal and was excluded from all evaluation steps. The other author declare that she has no conflict of interest.
Funding: None.
Informed Consent: Informed consents were taken from the participants of the study.

Cite as: Ustun N, Ovali F. Risk factors and outcomes of acute kidney injury in neonates with persistent pulmonary hypertension of the newborn. Medeni Med J. 2021;36:193-200.

ABSTRACT

Objective: *To identify the incidence of and risk factors for acute kidney injury (AKI) in neonates with persistent pulmonary hypertension of the newborn (PPHN) and to evaluate its association with neonatal outcomes.*
Method: *A total of 78 newborns with confirmed PPHN admitted to the neonatal intensive care unit of a university hospital between 2016 and 2020 were retrospectively analyzed. AKI was defined according to the modified neonatal Kidney Disease: Improving Global Outcomes criteria.*
Results: *Of 78 PPHN infants, AKI was found in 29.5% (23/78). Multivariate analysis indicated that male sex (OR 3.43 95% CI 1.03-11.48, p=0.04) and severe PPHN (OR 5.67 95% CI 1.55-20.68, p<0.01) were independently associated with increased risk for AKI. Infants with AKI had significantly higher mortality rate than infants without AKI (43.5% vs. 9.1%, p<0.01). Mortality rates in stage 1, stage 2 and stage 3 AKI were similar (36.4%, 57.1%, and 40%, respectively, p=0.68). Among survivors, AKI infants had significantly longer mechanical ventilation and lenght of stay than infants without AKI.*
Conclusion: *In infants with PPHN, AKI is a common complication and is associated with increased mortality, and longer mechanical ventilation and lenght of stay. Careful monitoring of kidney function in infants with PPHN, especially in males and those who had severe PPHN can help to improve patient outcomes.*

Keywords: *Persistent pulmonary hypertension of the newborn, acute kidney injury, mortality*

ÖZ

Amaç: *Yenidoğanın persistan pulmoner hipertansiyonu (PPHN) olan yenidoğanlarda akut böbrek hasarı (ABH) insidansını ve risk faktörlerini belirlemek, ve yenidoğan sonuçları ile ilişkisini değerlendirmek.*
Yöntem: *2016-2020 yılları arasında bir üniversite hastanesinin yenidoğan yoğun bakım ünitesine yatırılan doğrulanmış PPHN'si olan 78 yenidoğan retrospektif olarak incelendi. ABH tanısı, modifiye neonatal Kidney Disease: Improving Global Outcomes (KDIGO) kriterlerine göre konuldu.*
Bulgular: *78 PPHN bebeğinin %29.5'inde (23/78) ABH saptandı. Çok değişkenli analiz, erkek cinsiyetin (OR 3,43 %95 CI 1,03-11,48, p=0,04) ve şiddetli PPHN'nin (OR 5,67 %95 CI 1,55-20,68, p<0,01) bağımsız olarak ABH riskinde artış ile ilişkili olduğunu gösterdi. ABH olan bebeklerde ölüm oranı ABH olmayanlara göre anlamlı olarak daha yüksekti (%43,5'e karşı %9,1, p<0,01). Evre 1, Evre 2 ve Evre 3 ABH'deki ölüm oranları benzerdi (sırasıyla, %36,4, %57,1 ve %40, p=0,68). Hayatta kalanlar arasında, ABH olan bebeklerin mekanik ventilator ve hastanede yatış süreleri, ABH olmayan bebeklere göre daha uzun idi.*
Sonuç: *PPHN'li bebeklerde ABH yaygın bir komplikasyondur ve artan mortalite, daha uzun mekanik ventilasyon ve hastanede kalış süresi ile ilişkilidir. PPHN'li bebeklerde, özellikle erkeklerde ve şiddetli PPHN'si olanlarda böbrek fonksiyonunun dikkatli bir şekilde izlenmesi hasta sonuçlarını iyileştirmeye yardımcı olabilir.*

Anahtar kelimeler: *Yenidoğanın persistan pulmoner hipertansiyonu, akut böbrek hasarı, mortalite*

Received: 14 July 2021
Accepted: 10 September 2021
Online First: 30 September 2021

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INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is a clinical syndrome with heterogeneous etiologies. It occurs because of a failure in transition from fetal to postnatal circulation caused by abnormal pulmonary vasculature and growth. The reported incidence varies between 0.2 and 6.8 per 1000 live births[1]. Despite advances in the management of PPHN, about 7 to 39% of the affected infants still die[2-4]. The underlying causes of PPHN including perinatal asphyxia[5], congenital diaphragmatic hernia (CDH)[6], and infection[7] cause kidney injury. Nephrotoxic medications such as antibiotics and inotropes are often used in the clinical management of PPHN[8].

Acute kidney injury (AKI) is a frequent complication in newborns requiring admission to NICU and leads to increased mortality and morbidity[9]. The reported incidence of AKI in neonates varies widely, from 3.4 to 64%, depending on patient characteristics[10,11]. This population is particularly vulnerable to AKI since neonates have underdeveloped glomeruli and are prone to fluid disturbances and exposure to nephrotoxic drugs. Most of the neonatal AKI studies have focused on infants with very low birth weight, asphyxia, and congenital heart disease. However, there are limited studies addressing AKI in patients with PPHN[12,13].

Our objective was to determine the incidence of risk factors for AKI and to evaluate its association with neonatal outcomes in this study.

MATERIAL and METHODS

This retrospective study was conducted in the neonatal intensive care unit of a university hospital. Ethical approval was obtained from the Hospital Ethics Committee (Approval no: 2021/0288). Newborns with gestational age of >34 weeks and underwent echocardiography to confirm the diagnosis of PPHN between January 2016 and December 2020 were included. In order to confirm the diagnosis of PPHN, 2D-echocardiography was performed and reported by a pediatric cardiologist. PPHN was defined as elevated pulmonary artery pressure (PAP) estimated by measurement of tricuspid regurgitation jet velocity, or right to left or bidirectional shunt through ductus arteriosus (DA) or foramen ovale (FO). An estimated PAP <40 mmHg was classified as mild PPHN, between 40-60 mmHg as moderate PPHN, >60 mmHg as severe PPHN[14]. Other features were also evaluated to define the severity of PH: (i) intraventricular septum orientation (flattened septum was defined as mild to moderate PH and septum bowing into left ventricle was defined as severe PH); (ii) shunt direction at DA or FO (bidirectional shunt was defined sign of mild to moderate PH and right to left shunt was considered as severe PH); (iii) ventricular function (right ventricular dysfunction was considered as severe PH)[14]. Infants with congenital heart defects, major congenital anomalies and chromosomal disorders were excluded except CDH or pulmonary hypoplasia.

For each patient, SCr values measured as a part of routine biochemistry panel were evaluated for AKI. The diagnosis of AKI was made according to the modified neonatal Kidney Disease: Improving Global Outcomes definition (KDIGO) criteria, which take into account the increase in SCr compared to a reference value rather than a single cut-off value (Table 1)[15]. According to these criteria, AKI was defined as a SCr rise of ≥ 0.3 mg/dL within 48 hours or ≥1.5 times the reference value within seven days. Reference SCr was defined as the lowest previous SCr value. Urine output criteria were not applied due to inconsistent documentation.

Patient characteristics including demographics (sex, gestational age, birth weight, delivery mode, need for intubation at delivery room, and 1 and 5 minutes APGAR scores); etiology and severity of PPHN; and treatment options were recorded.

Potential risk factors before AKI onset were also collected, including the use of nephrotoxic medications (vancomycin, aminoglycosides, cephalosporins, carbapenems, and inotropes), insertion of central catheter, pneumothorax, and culture-proven sepsis. Mortality, duration of mechanical ventilation, and lenght of stay were noted as outcomes.

Statistical Analysis

IBM SPSS 22.0 was used for data analysis. Normally distributed continuous variables were compared using the Student's t-test. The duration of mechanical ventilation and hospital stay was compared using the Mann-Whitney U test. Discrete variables were compared using the chi-square test or Fischer's exact test. Variables with $p < 0.05$ in univariate regression analysis were selected for multivariate logistic regression model. A stepwise backward approach was applied to determine independent risk factors for AKI. Results were presented as odds ratio (OR) and their 95% confidence interval (CI). A p value of <0.05 represented a statistically significant result.

RESULTS

A total of 98 infants with confirmed PPHN was identified. A total of twenty infants, 13 with cyanotic congenital heart disease and seven with chromosomal disorders were excluded. The remaining 78 newborns (44 males and 34 females) were included in this analysis. The mean gestational age and birth weight were 38.1±1.6 weeks and 3000±605 g, respectively. The most frequent causes of PPHN were CDH (19) or pulmonary hypoplasia (5) followed by hypoxic ischemic encephalopathy (HIE) and meconium aspiration syndrome (MAS). Of 78 PPHN infants, 15 (19.2%) died before discharge.

Overall, 23 (29.5%) infants had evidence of AKI. Based on neonatal KDIGO definition, 11 (47.8%) infants had stage 1 AKI, 7 (30.4%) had stage 2 AKI and 5 (21.7%) had stage 3 AKI. The demographic and clinical characteristics of PPHN infants with and without AKI are shown in Table 1. Infants with AKI were more likely to be male and born by cesarean section. Apgar scores at 1 and 5 min were significantly lower in the AKI group than the non-AKI group. Patient characteristics such as gestational age, birth weight, rates of intubation at delivery room and the etiology of PPHN were similar between the AKI and non-AKI groups. The AKI group had a significantly higher rate of severe PPHN (82.6% vs. 50.9%, p<001) than the non-AKI group. The AKI group received significantly more high frequency ventilation (82.6% vs. 54.3% p=0.02) and inhaled nitric oxide (iNO) (91.3% vs. 69.1%, p=0.04) than the non-AKI group.

Possible risk factors before AKI onset in the study patients are presented in Table 3. There was no significant difference in exposure to nephrotoxic medication, central catheter placement, and culture-proven sepsis. Infants in the AKI group had a significantly higher rate of pneumothorax than infants without AKI (30.4% vs. 10.9%, p=0.03).

Table 1. Modified neonatal acute kidney injury Kidney Disease: Improving Global.

Stage	Serum creatinine (SCr)	Urine output
0	No change in SCr or increase < 0.3 mg/dL	≥ 0.5 mL/kg/h
1	SCr increase ≥ 0.3 mg/dL within 48 h or SCr increase ≥ 1.5-1.9 × reference[a] SCr within 7 d	< 0.5 mL/kg/h for 6-12 h
2	SCr increase ≥ 2-2.9 × reference[a] SCr	< 0.5 mL/kg/h for ≥ 12 h
3	SCr increase ≥ 3 × referencea SCr or SCr ≥ 2.5 mg/dL or receipt of dialysis	< 0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h

[a]: *Reference SCr was defined the lowest previous SCr*

Table 2. Demographic and clinical characteristics of PPHN infants with and without AKI.

	AKI (n=23)	No AKI (n=55)	P-value
Gestational age (weeks)*	38.5±1.7	38.1±2.2	0.42
Birth weight, (g)*	3064.9±558	2980.2±712	0.58
Male (n, %)	18 (78.3)	26 (47.3)	0.01
Born by C/S (n, %)	15 (65.2)	22 (40)	0.04
1 min APGAR score*	5.0±1.1	5.8±1.4	0.03
5 min APGAR score*	6.5±1.1	7.3±1.2	0.01
Intubation at delivery room (n, %)	15 (65.2)	27 (49.1)	0.19
Causes of PPHN (n, %)			
CDH or pulmonary hypoplasia	10 (43.5)	14 (25.5)	0.12
Hypoxic ischemic encephalopathy	7 (30.4)	10 (18.2)	0.23
Meconium aspiration syndrome	3 (13.0)	10 (18.2)	0.58
Transient tachypnea of newborn	1 (4.3)	9 (16.4)	0.15
Respiratory distress syndrome	0	5 (9.1)	0.13
Congenital pneumonia	1 (4.3)	5 (9.1)	0.47
Idıopathic	1 (4.3)	2 (3.6)	0.88
Echocardiography (n, %)			
Mild to moderate PPHN	4 (17.4)	28 (50.9)	<0.01
Severe PPHN	19 (82.6)	27 (49.1)	
Treatment modalities (n, %)			
Inhaled nitric oxide	21 (91.3)	38 (69.1)	0.04
High frequency ventilation	19 (82.6)	30 (54.5)	0.02
Sildenafil	15 (65.2)	25 (45.5)	0.11
Milrinone	8 (34.8)	9 (16.4)	0.07
AKI KDIGO classification (n, %)			
Stage 0	0	55 (100)	NA
Stage 1	11 (47.8)	0	
Stage 2	7 (30.4)	0	
Stage 3	5 (21.7)	0	
Mortality (n, %)	10 (43.5)	5 (9.1)	<0.01
Duration of mechanical ventilation (d)**	8.5 (7-13)	4.5 (3-9)	0.01
Duration of hospital stay (d)**	34.5 (28-46)	19 (16-32)	<0.01

AKI, acute kidney injury; NA, not applicable; PPHN, persistent hypertension of the newborn; C/S, cesarean section
**: presented as mean ± standard deviation*
***: presented as mean (interquartile range) and compared by Mann-Whitney U test.*

Table 3. Risk factors for AKI in PPHN infants with and wihout AKI.

	AKI (n=23)	No AKI (n=55)	P-value
Drug exposure (n, %)			
Vancomycin	10 (43.5)	18 (32.7)	0.38
Aminoglycosides	20 (87)	42 (76.4)	0.48
Cephalosporins	8 (34.8)	15 (27.8)	0.51
Carbapenems	6 (26.1)	11 (20)	0.55
Inotropes	22 (95.7)	50 (90.9)	0.47
Culture proven sepsis (n, %)	5 (21.7)	8 (14.5)	0.44
Pneumothorax (n, %)	7 (30.4)	6 (10.9)	0.03
Central catheter, (n, %)	18 (78.3)	37 (67.3)	0.33

Risk factors found to be associated with AKI in univariate analysis were entered into a multivariate model (Table 4). Logistic regression analysis revealed that male sex (OR 3.43 95%CI 1.03-11.48, p=0.04) and severe PPHN (OR 5.67 95% CI 1.55-20.68, p<0.01) were independently associated with an increased risk for AKI.

Table 4. Univariate analysis and multivariate model for risk factors for AKI in infants with PPHN.

Univariate analysis	OR (95% CI)	P-value	Multivariate analysis	OR (95% CI)	P-value
Male	4.01 (1.31-12.35)	0.01	Male	3.43 (1.03-11.48)	
Born by C/S	3.43 (1.21-9.69)	0.02	Born by C/S	2.93 (0.94-9.13)	0.04
1 min APGAR score	1.52 (1.03-2.23)	0.03	-	-	0.06
5 min APGAR score	1.79 (1.13-2.84)	0.01	-	-	-
Severe PPHN	4.93 (1.48-16.37)	<0.01	Severe PPHN	5.67 (1.55-20.68)	-
HFV	3.96 (1.19-13.16)	0.02	-	-	<0.01
INO	4.70 (1-22.33)	0.04	-	-	-
Pneumothorax	3.56 (1.05-12.18)	0.03	-	-	-
					-

Abbreviations: AKI, acute kidney injury; PPHN, persistent hypertension of the newborn OR, odds ratio; CI, confidence interval; C/S, cesarean section, HFV, high frequency ventilation; INO, inhaled nitric oxide.

Table 5. PPHN severity and mortality according to AKI stages in PPHN infants with AKI.

	AKI			
	Stage 1 (n=11)	Stage 2 (n=7)	Stage 3 (n=5)	P-value
PPHN Severity (n, %)				
Mild to moderate	2 (18.2)	1 (14.3)	1(20)	0.96
Severe	9 (81.8)	6 (85.7)	4 (80)	
Mortality (n, %)	4 (36.4)	4 (57.1)	2 (40)	0.68

The mortality rate was significantly higher in the AKI group compared with the non-AKI group (43.5% vs.9.1%, p<0.001). Among survivors, the AKI group had longer mechanical ventilation (p=0.01) and hospital stay (p<0.01) than the non-AKI group (Table 2). In PPHN patients with AKI who died, there was no significant relationship between AKI stages and PPHN severity or mortality (Table 4).

DISCUSSION

In this study, we found that AKI is a frequent complication in infants with PPHN. Male sex and severe PPHN identified by echocardiography were significantly associated with increased risk for AKI development in these patients. Also, AKI in PPHN infants was associated with increased mortality, longer mechanical ventilation, and longer hospital stay.

In our study, AKI occurred in 29.5% of PPHN infants. This incidence could be an underestimation due to not including urinary output criteria in the AKI definition. Also, some patients may have died before reaching the diagnostic criteria. Since we do not have data on fluid overload, its relationship with AKI development and outcomes could not be evaluated. However, the overall incidence in our study agreed with previous studies. Sheta et al.[12] evaluated 47 term infants with PPHN and reported an AKI rate of 34% by using modified KDIGO criteria. Kamolvisit et al.[13] found an AKI rate of 28.4% among 109 PPHN infants. The high incidence of AKI can be considered because of underlying causes of PPHN, which are associated with AKI. In several studies, meconium aspiration syndrome (MAS) was the most prevalent cause of PPHN[3,4]. In the current study, CDH was the most common cause of PPHN. This could be because our unit is a referral center for CDH. Although causes of PPHN did not differ significantly between infants with and without AKI, CHD, and HIE accounted for majority (73.9%) of AKI cases and both of them have high risks for AKI. Ryan et al.[16] reported that

AKI developed in 37% of CDH cases. Selewski et al.[5] found an AKI rate of 38% in HIE cases treated with therapeutic hypothermia.

In infants with PPHN, the degree of severity of PPHN is an important determinant of outcomes[17-19]. Data in the literature on the association between PPHN severity and AKI are limited. Sheta et al.[12] suggested a relationship between AKI and severe PPHN diagnosed by oxygenation index. In our study, severe PPHN diagnosed by echocardiography was associated with 5.7 fold-increased risk for AKI. We did not include oxygenation index data in this study since not all patients had arterial line. Severe PPHN indicates hypoxemia and the association between severe PPHN and AKI can be explained by hypoxic injury in lungs and kidneys. Animal studies showed increased hypoxia-induced factor (HIF) activity in PPHN vascular cells[20]. Although the role of HIF in the pathogenesis of neonatal AKI has not yet been addressed, its role in renal damage was discussed in experimental studies[21]. The reactive oxygen species contribute to the development of PPHN[22] and AKI[23]. However, pathophysiological interactions occurring in both conditions need to be elucidated. Further studies on PPHN and AKI, including oxygenation index and echocardiographic components of PPHN severity, would be useful.

The association between male sex and AKI was reported in different neonatal populations[7,24]. In our study, we found that male sex was a risk factor for AKI in infants with PPHN, in accordance with a previous study[13]. However, Momtaz et al.[25] reported a female dominance in their neonatal AKI group. There is not much known about how gender relates to kidney function. More research on this feature of AKI in neonatal population is needed.

Previous studies have reported a high rate of PPHN following cesarean delivery[26]. Also, the need for cesarean section indicating fetal distress was reported as a risk factor for neonatal AKI[9]. In our study, although not significant, there was an increased AKI risk with cesarean delivery (p=0.06). However, in the study of Kamolvisit el al.[13], cesarean delivery was reported as a protective factor for AKI in infants with PPHN. Future studies regarding the impact of cesarean delivery on PPHN-associated AKI would be helpful in the evaluation of these cases.

In PPHN patients, the availability of new treatment options affects the mortality outcome. Studies from developed countries reported that PPHN continues to be an important clinical problem with a mortality rate ranging between 5 and 15% [2]. High mortality rates up to 40% were reported from the developing world[27]. The mortality rate of 19.2% in our cohort is compatible with the literature. In this study, we used advanced treatment options, such as HFV and iNO in addition to sildenafil. However, ECMO treatment, associated with significantly improved survival in PPHN[28], was not available in our hospital during the study period.

The association between AKI and decreased survival was reported in many studies of neonates with various conditions[5,9]. Nakwan et al.[29] evaluated 119 infants with PPHN and found a higher mortality in cases complicated by AKI. In this study, patients with AKI had a higher risk of death than those without AKI (OR 7.7). Among the patients with AKI who died, mortality rates in AKI stage 1, stage 2 and stage 3 did not significantly differ. This may be due to the similar PPHN severity rates in AKI stages in these patients. In fact, renal injury itself is not directly responsible for death. Disease severity, AKI, and mortality are probably interdependent and the cause of death is typically multisystemic or cardiorespiratory rather than exclusively renal originated. Among survivors, PPHN infants with AKI had significantly longer mechanical ventilation support and lenght of stay. In preterm neonates, AKI was related to prolonged need for mechanical

ventilation and chronic lung disease[30]. Animal studies showed that kidney injury impairs lung hemostasis by increasing systemic inflammatory response and pulmonary neutrophil activity[31,32]. This likely increases the sensitivity of lungs to ongoing injury in PPHN patients.

This study has several limitations. First, the retrospective nature of the study increases the possibility of missing confounding factors. Second, we defined AKI based on SCr, which is a poor marker of kidney injury in neonates[33]. Third, results were monitored until discharge in our study. For long-term AKI results, further studies with larger sample sizes are needed.

CONCLUSION

In patients with PPHN, AKI is a frequent complication and is associated with increased mortality, and longer mechanical ventilation and lenght of stay. To improve patient outcomes, it is critical to perform careful monitoring of kidney function, especially in males and those who had severe PPHN.

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