



Association of Acute Kidney Injury with Bronchopulmonary Dysplasia in Preterm Infants

Prematüre Bebeklerde Akut Böbrek Hasarının Bronkopulmoner Displazi Gelişimindeki Etkisi

© Saime Hacer OZDEMİR, © Husnu Fahri OVALI

Medeniyet University Faculty of Medicine, Department of Pediatrics, Istanbul, Türkiye

ABSTRACT

Objective: Bronchopulmonary dysplasia (BPD) is among the most common complications of prematurity and is associated with high morbidity and mortality rates. Acute kidney injury (AKI) is also commonly observed in premature infants and significantly increases morbidity and mortality. Studies have shown that systemic changes in AKI may also trigger lung damage.

Methods: This study aimed to determine the effects of AKI on the development of BPD in preterm infants with a postconceptional age of ≤ 32 weeks and/or birth weight of ≤ 1500 grams. The relationship between demographic features and accompanying perinatal and postnatal morbidities among the patients was investigated.

Results: The incidence of BPD in infants with AKI was 52.6% (10 of 19 infants) and 38.3% (61 of 140 infants) in infants without AKI. In infants who developed BPD, the rate of AKI did not vary notably between babies born at ≤ 28 weeks and those born at >28 weeks [$n=9$, 17.3% (9 of 52 infants) and $n=1$, 5.3%, (1 of 19 infants) respectively] of gestation ($p>0.05$).

Conclusions: AKI was associated with a greater need for resuscitation at birth, a greater need for invasive mechanical ventilation, fewer ventilator-free days, and a higher incidence of sepsis, patent ductus arteriosus, and necrotizing enterocolitis in premature infants. It was also more frequently associated with fluid-electrolyte imbalance, blood pressure, and hemodynamic disorders in the first postnatal week. The rate of BPD development was higher in infants with AKI, but this disparity was not statistically notable ($p>0.05$).

Keywords: Prematurity, acute kidney injury, bronchopulmonary dysplasia, organ crosstalk

ÖZ

Amaç: Bronkopulmoner displazi (BPD), prematüre doğan bebeklerde en sık görülen komplikasyonlarından biridir ve yüksek morbidite ve mortalite oranlarıyla ilişkilidir. Akut böbrek hasarı (ABH), prematüre bebeklerde oldukça yaygındır. ABH prematüre bebeklerde morbidite ve mortaliteyi önemli ölçüde artırır. Çalışmalar ABH'de görülen sistemik değişikliklerin akciğer hasarını tetikleyebileceğini göstermiştir.

Yöntemler: Bu çalışmada, gestasyon haftası ≤ 32 hafta ve/veya doğum tartısı ≤ 1500 gram olan prematüre bebeklerde ABH'nin BPD gelişimine etkisinin belirlenmesi amaçlanmıştır. Bu hastaların demografik özellikleri ile eşlik eden perinatal ve postnatal morbiditeler arasındaki ilişki araştırılmıştır.

Bulgular: ABH'li bebeklerde BPD görülme oranı %52,6 (19 bebekten 10'u), ABH olmayan bebeklerde ise %38,3 (140 bebekten 61'i) idi. BPD gelişen bebeklerde ABH görülme oranı, ≤ 28 hafta doğan bebekler ile >28 hafta doğan bebekler (sırasıyla $n=9$, %17,3 (52 bebekten 9'u) ve $n=1$, %5,3 (19 bebekten 1'i)) kıyaslandığında anlamlı farklılık göstermedi ($p>0,05$).

Sonuçlar: ABH, doğumda daha fazla resüsitasyon ihtiyacı, daha fazla invaziv mekanik ventilasyon ihtiyacı, daha az ventilatörsüz gün ve prematüre bebeklerde daha yüksek sepsis, patent duktus arteriosus ve nekrotize enterokolit insidansı ile ilişkiliydi. Bununla birlikte ABH; doğum sonrası ilk haftalarda sıvı-elektrolit dengesizliği, kan basıncı ve hemodinamik bozukluklarla daha sık ilişkili bulundu. ABH gelişen bebeklerde BPD gelişme oranı daha fazla olmakla birlikte bu fark istatistiksel olarak önemli değildi ($p>0,05$).

Anahtar kelimeler: Prematürite, akut böbrek hasarı, bronkopulmoner displazi, organ çapraz etkileşimi

Address for Correspondence: S.H. Ozdemir, Medeniyet University Faculty of Medicine, Department of Pediatrics, Istanbul, Türkiye
E-mail: ozdemirshacer@gmail.com **ORCID ID:** orcid.org/0009-0009-3168-4445

Received: 22 April 2024
Accepted: 12 June 2024
Online First: July 2024

Cite as: Ozdemir SH, Ovali HF. Association of Acute Kidney Injury with Bronchopulmonary Dysplasia in Preterm Infants. Medeni Med J. 2024;39:152-160



Copyright© 2024 The Author. Published by Galenos Publishing House on behalf of Istanbul Medeniyet University Faculty of Medicine. This is an open access article under the Creative Commons AttributionNonCommercial 4.0 International (CC BY-NC 4.0) License.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is among the most common diseases in prematurely born infants and is associated with high morbidity and mortality in the first years of life. BPD is also linked to lifelong impaired lung function and medical costs¹.

Many complex factors caused by the immaturity of organs and systems have been identified in the pathophysiology of BPD. Factors such as lung immaturity, infections, barotrauma caused by mechanical ventilation (MV), fluid overload, and inflammation have been shown to be effective in the pathogenesis of BPD².

Conversely, acute kidney injury (AKI)-induced systemic inflammation is observed in almost 40% premature infants³. AKI alone is associated with higher mortality in premature infants and chronic renal failure in both childhood and adult age groups⁴. Increased infection rates and the use of nephrotoxic drugs in preterm infants are among the factors associated with AKI⁵.

Studies conducted in recent years have shown that systemic changes in AKI may also trigger lung damage. Although the mechanism underlying this phenomenon has not been fully understood, results in animal studies indicate that there is a mutual interaction between kidney and lung⁶⁻⁹.

AKI may have deleterious effects on lung physiology due to fluid imbalance, changes in vascular tone and acid-base imbalance. Kidney damage also activates extrarenal inflammatory pathways and impairs lung function. Conversely, alveolar gas exchange disorders seen in lung diseases affect kidney function and cause homeostatic deterioration¹⁰. Hypoxia and hypercapnia can directly affect renal vascular tone and cause renal damage¹⁰⁻¹². Prolonged MV in infants who develop BPD affects renal function as a result of neurohormonal changes, blood gas disorders and hemodynamic disorders¹³.

This study aimed to determine the effects of AKI on the development of BPD in premature infants.

MATERIALS and METHODS

Premature infants with a postconceptional age of ≤32 weeks and/or a birth weight of ≤1500 grams, who developed AKI were included.

Infants with congenital heart disease, chromosomal disorders/diseases, those who died within the first 48 hours, those with severe kidney and/or urinary system anomalies or abdominal wall defects, patients whose

families did not give consent, and patients whose data were missing at the end of the study were not included in the study.

Demographic information (gender, gestational age, birth weight, etc.) of the patients, antenatal steroid use, maternal morbidities (preeclampsia, gestational diabetes mellitus, chorioamnionitis, etc.), and other perinatal morbidities, cord blood gas values, 5th minute Apgar scores, presence of intrauterine growth restriction, multiple pregnancy, and need for oxygen, resuscitation, and intubation at birth were recorded.

Serum creatinine, urea, sodium, potassium, C-reactive protein, and blood gas values, which are routinely monitored in patients within the first 15 days of life, were recorded.

Daily weights, weight changes (+/- grams/day) of patients, and weight change rates at the end of the 15th day of life were investigated. If the weight on the 15th day had increased by more than 5% of the birth weight, it was considered weight gain; if there had been a loss of more than 5% of the birth weight, it was considered weight loss.

The total daily urine and fluid intake were recorded and evaluated as normal, oliguria (<1 mL/kg/hour) or anuria (no urine in the last 24 hours). Nephrotoxic drug use in infants within the first 15 postnatal days was also recorded.

Blood pressure (BP) was measured daily in the infants. Neonatal hypertension was defined as persistent systolic and/or diastolic BP above the 95th percentile for postmenstrual (also referred to as postconceptional) age. Hypotension was defined as BP below the 5th percentile for postconceptional and postnatal ages. Measurements between the 5th and 95th percentiles according to postconceptional age and postnatal age were considered within the normal range.

Morbidities that developed in the patients [respiratory distress syndrome, BPD, pneumonia, sepsis, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), retinopathy of prematurity, etc.] were recorded.

AKI was diagnosed, and patients were categorized considering Kidney Disease: Improving Global Outcomes (KDIGO) criteria¹⁴. The patients' need for oxygen and/or assisted breathing on the 28th postnatal day and the 36th postconceptional week was recorded. The diagnosis of BPD was made according to the diagnostic criteria established by NIH (National Institute of Child Health and Human Development Workshop) and the patients were classified accordingly¹⁵.

The rate of BPD development in premature babies born with a postconceptional age ≤ 32 weeks and/or a birth weight ≤ 1500 grams, in the patients who did and did not develop AKI according to the KDIGO classification, and the relationship between demographic features and accompanying perinatal and postnatal morbidities among these patient groups were investigated. Ethical approval was obtained from the Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (decision no: 2021/0410, date: 25.08.2021). Written informed consent was obtained from the families of the patients who participated in the study.

Statistical Analysis

Descriptive statistics were analyzed by evaluating mean, standard deviation, median, lowest, highest, frequency, and ratio values. Kolmogorov-Smirnov test was used to determine the distribution of variables. Independent sample t-test and Mann-Whitney U test were used to analyze quantitative independent data. The chi-square test and Fisher’s exact test were used to analyze qualitative independent data. SPSS 28.0 program was used in the analysis.

RESULTS

During the study period, 172 infants were born at or before 32 weeks of gestation and/or with a birth weight of 1500 g or less. Thirteen infants who did not meet the inclusion criteria were excluded, and the data of 159 infants were analyzed, including 79 girls (49.7%) and 80 boys (50.3%) (Figure 1). The mean gestational age of the infants was 29+2 weeks ± 2 days, and the mean birth weight was 1200 g. The mean 5th minute Apgar score was 7.3 $\pm$ 1.5. The mean duration of intubation during the first 15 days of life was 7.2 days $\pm$ 5.5 days. 18 (11.3%) patients died during intensive care (Table 1).

The most common electrolyte abnormality in the first 15 days of life was hyponatremia (58.8%, 20 of 34 infants), and the most common blood gas disorders were metabolic acidosis (60.3%, 35 of 63 infants) and respiratory acidosis (41.4%, 24 of 63 infants). Daily urine output was normal in 86.2% (137 of 159 infants), whereas 2.5% (4 of 159 infants) were anuric and 11.3% (18 of 159 infants) were oliguric. The mean daily fluid intake of the infants was 125 $\pm$ 18.5 mL/kg/day (minimum-maximum: 67-174 mL/kg/day, median: 125 mL/kg/day).

The rate of AKI was 11.9% (19 of 159 infants), 9 of them being stage 2 (47.3%, n=9). BPD developed in 44.7% (71 of 159 infants) of the patients. The rate of BPD among infants who developed AKI was 52.6% (10 of 19 infants) (Figure 2).

Gestational age, birth weights and 5th minute Apgar scores were notably lower in infants with AKI than in those without AKI ($p<0.05$). Although the rate of infants with AKI who exceeded their birth weight on the 15th day was higher (n=11, 84.6%), the rate was not notably higher than that of infants without AKI ($p>0.05$). The rate of intubation requirement and the total intubation time in the first 15 days were significantly higher in infants with AKI ($p<0.05$) (Table 2). Eleven of the infants with AKI died during neonatal intensive care unit follow-up, and this rate was significantly higher than the infants without AKI ($p<0.05$) (Table 2). The rate of antenatal steroid administration was comparable in both groups.

The mean daily fluid intake (130.5 $\pm$ 17.7 mL/kg/g) was significantly higher in infants with BPD ($p<0.05$) compared to non-BPD infants (121.2 $\pm$ 18.2 mL/kg/day).

The total daily fluid intake of infants with AKI (mean: 127.3 $\pm$ 21.4 mL/kg/day, median: 127 mL/kg/day) and those without AKI (mean: 125.1 $\pm$ 18.2 mL/kg/day, median:

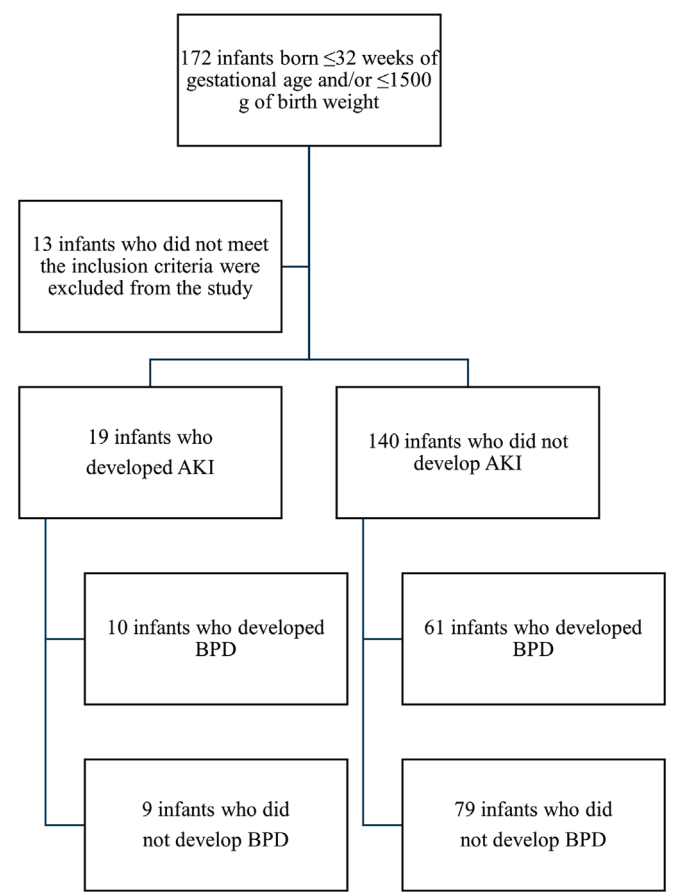


Figure 1. Flow chart of the study.
AKI: Acute kidney injury, BPD: Bronchopulmonary dysplasia

125 mL/kg/day) did not show any statistically notable variation ($p>0.05$).

There was no statistically notable variation with regard to oxygen need in the delivery room between patients with and without AKI ($p>0.05$). In patients with AKI, the rate of positive pressure ventilation (PPV) use at birth, the need for cardiopulmonary resuscitation in the delivery room, and the need for intubation in the delivery room

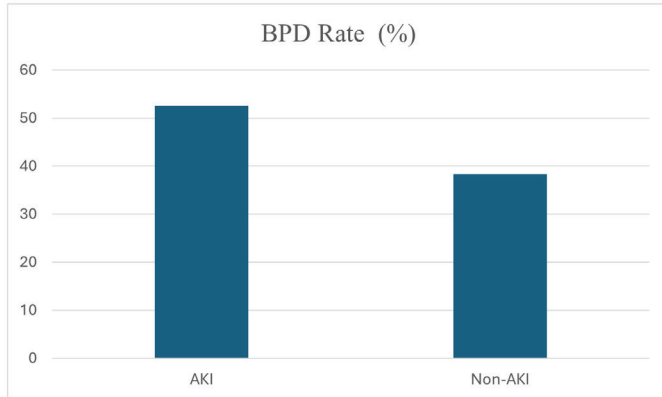


Figure 2. Bronchopulmonary dysplasia rate in infants with or without acute kidney injury (52.6 vs. 38.3%).

AKI: Acute kidney injury, BPD: Bronchopulmonary dysplasia

Table 1. Demographic data of the study group (n=159).

Gestational age (weeks)	29.1±2.5 (23-26)
Male	80 (50.3%)
Female	79 (49.7%)
Birth weight (grams)	1184.1±416.1 (488-2313)
5 th minute Apgar score	7.3±1.5 (1-10)
Intubation time within 15 days	7.2±5.5 (1-15) days
Death	18 (11.3%)

were markedly higher than those in the non-AKI patients ($p<0.05$) (Table 3). The rate of electrolyte, blood gas, urine output abnormalities, and BP abnormalities were observed more frequently in patients with AKI ($p<0.05$) (Table 3).

Clinical findings of respiratory distress syndrome were significantly longer in babies with AKI ($p<0.05$). The rate of surfactant treatment in infants with AKI was significantly higher than those in non-AKI babies ($p<0.05$). The rates of sepsis, pneumonia, hemodynamically significant PDA, and NEC were notably higher in babies with AKI were notably higher than the non-AKI infants ($p<0.05$) (Table 4).

The mean gestational age of non-AKI infants who developed BPD was significantly lower (27.5 vs. 30 weeks; $p<0.05$).

Among the non-AKI infants, the birth weight and 5th minute Apgar scores of the patients with BPD were markedly lower than those of the non-BPD infants ($p<0.05$). Additionally, the rate of maternal preeclampsia was significantly higher in patients with BPD (16 of 61 infants, 29.5%) ($p<0.05$). The rate of PPV application in the delivery room (47 of 61 infants, 77%) and the rate of need for intubation in the delivery room (33 of 61 infants, 54.1%) were higher in the group that developed BPD in non-AKI infants ($p<0.05$).

Among non-AKI infants who developed BPD, a higher incidence of electrolyte abnormalities (15 of 61 infants, 24.6%), blood gas abnormalities (n=32 of 61 infants, 54.2%), urine output abnormalities during the first 15 days of life (decrease in the amount of urine: 5 of 61 infants, 8.2%), rate of BP abnormalities (10 of 61 infants, 16.4%), and the use of nephrotoxic drugs (57 of 61 infants, 93.4%) ($p<0.05$) were observed. The surfactant treatment rate in non-AKI infants was significantly higher in patients with BPD (54 of 61 infants, 88.5%) ($p<0.05$). Among non-AKI

Table 2. Demographic features of infants who did and did not develop acute kidney injury.

	AKI (-)		AKI (+)		p-value
	Mean ± SD/n, %	Median	Mean ± SD/n, %	Median	
Gestational age (weeks)	29.4±2.4	29.7	26.8±2.1	27.4	0.000
Birth weight (grams)	1241.7±404.2	1254.5	759.7±204.5	695.0	0.000
Apgar score 5 th minute	7.4±1.4	8.0	6.1±1.7	6.0	0.002
Need for intubation within the first 15 days of life	58 (41.4%)		16 (84.2%)		0.000
Total intubation period during the first 15 days of life (days)	6.2±5.3	5.0	11.0±4.4	13.0	0.001
Death rate	7 (5.0%)		11 (57.9%)		0.000

AKI: Acute kidney injury, SD: Standard deviation

n (%)		AKI (-)	AKI (+)	p-value
		n (%)		
PPV at birth	(+)	87 (62.1%)	18 (94.7%)	0.005^{X2}
	(-)	53 (37.9 %)	1 (5.3%)	
Resuscitation at birth	(+)	3 (2.1%)	4 (21.1%)	0.004^{X2}
	(-)	137 (97.9%)	15 (78.9%)	
Intubation at birth	(+)	56 (40.0%)	14 (73.7%)	0.006^{X2}
	(-)	85 (60.0%)	5 (26.3%)	
Electrolyte abnormalities	(+)	23 (16.4%)	11 (57.9%)	0.000^{X2}
	(-)	117 (83.6%)	8 (42.1%)	
Blood gas abnormalities	(+)	42 (33.9%)	16 (88.9%)	0.000^{X2}
	Normal	82 (66.1%)	2 (11.1%)	
Urine output	Anuria	0 (0%)	4 (21.1%)	0.000^{X2}
	Oliguria	6 (4.3%)	12 (63.2%)	
Blood pressure	Hypotensive	2 (1.4%)	9 (47.4%)	0.000^{X2}
	Hypertensive	12 (8.6%)	4 (21.1%)	

^{X2}Chi-square test (Fisher's exact). AKI: Acute kidney injury, PPV: Positive pressure ventilation

	AKI (-) (n=140)		AKI (+) (n=19)		p-value
	Mean ± SD/n-%	Median	Mean ± SD/n-%	Median	
Surfactant treatment	90 (64.3%)		17 (89.5%)		0.028^{X2}
RDS recovery day	4.3±4.7	3.0	7.5±5.2	5.0	0.001^m
Sepsis	106 (75.7%)		19 (100%)		0.015^{X2}
Total number of days with sepsis	13.0±9.2	10.0	15.8±9.0	17.0	0.083 ^m
Patent ductus arteriosus	32 (22.9%)		13 (68.4%)		0.000^{X2}
Necrotizing enterocolitis	15 (10.7%)		9 (47.4%)		0.000^{X2}

^mMann-Whitney U test, ^{X2}Chi-square test (Fisher test). AKI: Acute kidney injury, SD: Standard deviation

infants, the incidence of sepsis (56 of 61 infants, 91.8%) and total sepsis duration (16.1±10.1 days, median: 13.5) were markedly higher in patients with BPD ($p<0.05$).

Among non-AKI infants, the rate of hemodynamically significant PDA (25 of 61 infants, 41%) and NEC (13 of 61 infants, 21.3%) and daily fluid intake (130.4±18.9 mL/kg/g, median: 130 mL/kg/g) were significantly higher in infants with BPD ($p<0.05$). The duration of sepsis was found to be considerably ($p<0.05$) higher in the group that developed BPD (mean: 21.8±6.8 days) than in those who did not develop BPD (mean: 16.1±10.1 days).

DISCUSSION

AKI usually occurs as a complication of damage to organs, such as the lungs, heart, liver, intestine, and brain. However, the information obtained in recent studies supports that a damaged kidney can also be the reason

for dysfunction in other organs¹⁶. AKI is a serious condition that may worsen prognosis, especially in critically ill patients. In our study, we found that AKI caused an important increase in the incidence of NEC and PDA in infants ($p<0.05$). Similar findings were reported by Starr et al.¹⁷.

In Jetton et al.'s³ multicenter, multinational observational cohort study, AKI was found to be common in newborns with congenital heart disease, sepsis, and hypoxic ischemic injury, in infants receiving extracorporeal membrane oxygenation, and in very low birth weight infants. In the same study, it was stated that newborns and children with AKI had a worse prognosis than those without AKI³. These findings also support the results of our study.

The same authors found that compared with non-AKI infants, infants with AKI belonged to a higher birth

weight category and had higher hospitalization rates for hypoxic ischemic encephalopathy, seizures, congenital heart disease, NEC, and surgical evaluation³. In our study, the incidence of NEC was greater in infants who had AKI than in those who did not ($p<0.05$). This suggests that pathophysiologic factors that predispose patients to AKI may also be instrumental in the development of NEC. The main pathway for these factors is inadequate intestinal circulation, leading to hypoxia.

The rate of AKI in preterm infants was reported to be 19% in a single-center study based on retrospective and prospective data⁴. In our single-center observational cohort study, the rate of AKI development in the first 15 days of life in infants born at or before 32 weeks of gestation and/or with a birth weight of 1500 g or less was 11.9%, which was comparable to other studies^{1,2,4}. Hypotension due to impaired cardiac function or inadequate autoregulatory response of the peripheral vasculature in these tiny infants, as well as delicate fluid balance, which may be affected by various renal or extra-renal factors, leads to the cause of AKI.

In a prospective study, Koralkar et al.⁴ examined the relationship between AKI and mortality in preterm infants born 1500 g in terms of incidence and outcomes and 41 of 229 (18%) patients were found to have AKI. In the same study, infants with AKI had a lower birth weight (mean 702 g vs. 1039 g) and gestational age (mean 25 weeks vs. 28 weeks). Infants with AKI had lower 1st and 5th minute Apgar scores and a higher need for umbilical arterial catheter, MV support, and inotropic support⁴. This finding also supports the notion that the more premature an infant is, the more are the complications of prematurity because the development of organ systems and balancing regulations are still immature.

In our study, gestational ages (mean: 26.8 weeks) and birth weights (mean: 759.7 g) of infants with AKI were found to be lower than those of non-AKI infants ($p<0.05$). Additionally, the 5th Apgar score of the AKI group was notably lower than that of the non-AKI group ($p<0.05$). In this case, hypoxia in the immediate postnatal period may have predisposed the infant to AKI.

We also observed that invasive MV requirement in the first 15 days (84.2%) and total invasive MV duration in the first 15 days (mean: 11 days) were significantly higher in patients with AKI than non-AKI patients ($p<0.05$). These results were compatible with those of Askenazi et al.¹⁸ and Starr et al.¹⁷. Increased need for MV is associated with immaturity in infants, as well as possible complications such as hypoxia, sepsis, and NEC. Therefore, increased rates of AKI may be expected in infants who develop

these complications.

In their study published in 2005, Abosaif et al.¹⁹ emphasized that AKI in intensive care units was due to the combined effects of hypotension, sepsis, and toxic exposure. Sepsis is a well-known risk factor for the development of AKI and is known to cause 35-50% of AKI cases in intensive care units^{20,21}. In our study, the rate of suspected or proven sepsis in preterm infants in the neonatal intensive care unit was found to be 78.6%. There are studies indicating that among patients with AKI, the mortality rate is higher in those with sepsis compared to those without¹⁹. Starr et al.¹⁷ also found that the rate of sepsis was higher in preterm infants who developed AKI ($p<0.001$). As stated above, this finding is also an expected finding, since sepsis is associated with hypotension and/or toxic exposure, leading to deterioration of the infant, derangement of fluid status, and impairment of renal function.

Koralkar et al.⁴ reported that infants with preeclampsia and maternal hypertension developed AKI at a lower rate. In that study, it was found that most infants with AKI had a birth weight of <750 g [29 of 41 (70%)] and a gestational age of less than 26 weeks of gestation [30 of 41 (73%)]⁴. A similar result was reported by Askenazi et al.¹⁸ in their study published in 2013. They suggested two possible explanations for this finding¹⁸. First, they stated that preeclampsia may indicate a response to a maternal problem rather than a primarily fetal/neonatal problem. Thus, the cause of prematurity or initial morbidities may be the mother, not the baby. Another possibility is that preeclampsia may have a protective effect against AKI. They hypothesized that small and repeated ischemic events may prevent AKI due to ischemic preconditioning. Some other studies have shown similar predictions²²⁻²⁴. In our study, there was no marked diversity in the rates of maternal preeclampsia, gestational diabetes mellitus, and chorioamnionitis between patients with and without AKI ($p>0.05$). The low rate of preeclampsia in our cohort was attributed to the small number of cases in our group.

The rate of BPD among babies born at 32 and/or earlier gestational weeks and with a birth weight of 1500 g or less was 44.7%. There was no significant difference in infants born before or after 28 weeks of gestation. These findings are consistent with other studies^{17,25}. The association between BPD and renal function is another subject that should be addressed in depth in future studies.

For very-low-birth-weight newborns, the first week of life is a critical transition period. During this transition period, fluid and electrolyte imbalances can affect many

organs and systems²⁶. Especially the lungs affected by MV, inflammation, and left-to-right shunt due to PDA; are highly prone to damage from these fluid and electrolyte imbalances and may be related to the development of BPD. However, in our study, no relationship was found between the electrolyte anomalies of infants and the rate of BPD development. This suggests that electrolyte abnormalities alone may not be a risk factor for BPD. However, they may be significant in patients with fluid imbalances.

Excessive fluid intake has been shown to cause the development of clinically significant PDA and congestive heart failure^{27,28}. It has been suggested that this may also play a role in the pathogenesis of BPD. Arikan et al.²⁹ found that fluid overload was associated with an increase in the duration of MV. Santschi et al.³⁰ also highlighted similar findings and showed the relationship between fluid balance and pulmonary outcomes in critically ill patients. In a retrospective cohort study of 1382 extremely low birth weight newborns by Oh et al.³¹, it was suggested that higher fluid intake and less weight loss in the first 10 days of life were associated with an increased risk of BPD.

Askenazi et al.¹⁸, in their study on infants with a postconceptional age >34 weeks and birth weight >2000 g, found that fluid excess in the first 3 days of life was higher in babies with AKI in contrast to those who did not develop AKI. We did not detect any notable difference between the total amount of fluid taken in the first 15 days of life and the weight on the 15th day of life in our study group. Our unit's fluid protocol requires a more restricted approach, which might have prevented significant differences between the two groups. However, the mean total daily fluid intake of infants in the first 15 days of life was significantly higher (130 mL/kg/g, $p=0.003$) in our infants who developed BPD, which was comparable to that of other studies. Bell and Acarregui³² found that limited water intake remarkably increased postnatal weight loss and reduced the risk of PDA and NEC.

In our study, the weights of infants who developed BPD were evaluated on the 15th postnatal day, and 67.6% were found to have exceeded their birth weight (> birth weight +5% of birth weight), and this rate was not found to be significantly higher than that of infants without BPD. This finding was also attributed to the restrictive fluid protocol in our unit.

AKI is known to negatively affect the lungs through many mechanisms, including impaired fluid homeostasis, dysregulation of angiogenesis, and disruptions in acid-base and electrolyte balance¹⁷. These effects lead to excessive extravascular fluid, secondary inflammatory

reactions, more capillary-alveolar permeability, and disruption of the epithelial barrier, resulting in worsened lung dysfunction and disrupted gas exchange.

Complications such as pulmonary edema may develop in patients with AKI, and as a result, respiratory failure and the need for MV may occur³³. This interaction is thought to be secondary to inflammatory reactions, oxidative stress, and increased vascular permeability in the lungs that occur with the increase in immune system mediators³³.

Damage caused by chemical mediators released into the bloodstream has been proposed as the mechanism of lung-induced kidney damage³³. Additionally, the kidneys are extremely sensitive to changes in oxygen, and even a small amount of hypoxia can cause the kidneys to lose their autoregulation mechanisms. Similarly, hypercapnia secondary to acute lung injury causes vasoconstriction in the renal vascular network and activation of the renal angiotensin aldosterone system³³.

The functions of the lung as a respiratory organ include not only gas exchange but also immune modulation, hematopoietic, secretory, and metabolic function regulation, and under physiological conditions, this contributes to kidney and lung crosstalk¹⁶. The lungs and kidneys work together to maintain fluid acid-base balance by regulating BP via the renin-angiotensin-aldosterone system and bicarbonate and carbon dioxide concentrations via kallikrein-kinin¹⁶.

Under pathological conditions, kidney-lung crosstalk mechanisms include inflammatory reactions (e.g., unbalanced immune reactions and increased inflammatory cytokine release, etc.) and the disruption of fluid balance caused by kidney or lung damage (e.g., fluid overload, uremic toxin retention, hypoxia, and hypercapnia etc.)¹⁶.

AKI negatively affects the lungs mainly through increased respiratory failure, the need for invasive MV, and associated respiratory system complications^{24,33-35}. Chertow et al.³⁶ concluded that patients with AKI were more than twice as likely to develop respiratory failure and nearly three times more likely to die than those without AKI. A similar result was obtained in our study, and this data was thought to be suggestive that improvement from lung dysfunction is also affected by kidney damage.

AKI is associated with increased permeability, inflammatory cell infiltration, and increased oxidative stress in the lungs¹⁰. Lung damage can also trigger kidney damage, and one of the most important reasons for this is that the kidneys are very sensitive to minimal oxygen changes³³.

van den Akker et al.³⁷ found that MV increased the incidence of AKI by 3 times. There is strong evidence of MV-induced hemodynamic changes and systemic mediator release³⁷. In our study, the rate of invasive MV and total intubation time in the first 15 days were found to be markedly higher in the group that developed AKI among infants who developed BPD ($p < 0.05$). This result indicates that invasive MV may be a risk factor for AKI, and this finding is consistent with the data presented in the literature. However, it may be related to not only the MV per se but also the conditions that necessitate MV, such as sepsis, pneumonia, and respiratory distress syndrome.

Grigoryev et al.⁶ tested the hypothesis that AKI induces a strong inflammatory response and produces distinct genomic changes in the kidney and lung. Clinical studies have demonstrated a strong association between AKI and extrarenal organ dysfunction, and more recent animal studies have demonstrated a significant causal effect of AKI on remote organ dysfunction⁶. Recent studies have shown that there may be many negative crosstalk interactions between AKI and other organs because of imbalances in the metabolism of immune, inflammatory, and soluble mediators^{8,9,38}. These mechanisms also explain why AKI may cause remote organ dysfunction in infants.

The major limitation of our study is the small sample size. Due to low numbers, logistic regression analysis could not be performed to delineate the effects of many factors that are instrumental in the development of BPD.

In our study, AKI was found to be associated with a greater need for resuscitation at birth, a greater need for invasive MV, fewer ventilator-free days, and a higher incidence of sepsis, PDA, and NEC in preterm infants. It was also associated with more frequent fluid-electrolyte imbalance, BP abnormalities, and hemodynamic disorders in the first postnatal week.

In infants with BPD, more resuscitation needs at birth, more invasive MV needs, fewer ventilator-free days, and a higher incidence of sepsis, pneumonia, PDA, and NEC were observed. The daily fluid intake was also higher in infants with BPD. This finding is consistent with other studies reporting that excess fluid poses a risk of BPD during this period of life.

CONCLUSION

In conclusion, the rate of BPD development was higher in babies who developed AKI. Although not statistically significant, we believe that the difference is important. We believe that a sound evaluation of the common

risk factors for such morbidities, which are frequently encountered in preterm infants, is important in terms of long-term organ health and measures to be taken to ensure optimal growth and development in this sensitive patient group. More studies are needed to explain the exact relationship between AKI and BPD.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (decision no: 2021/0410, date: 25.08.2021).

Informed Consent: Written informed consent was obtained from the families of the patients who participated in the study.

Author Contributions

Surgical and Medical Practices: S.H.O., H.F.O., Concept: S.H.O., H.F.O., Design: S.H.O., H.F.O., Data Collection and/or Processing: S.H.O., Analysis and/or Interpretation: S.H.O., H.F.O., Literature Search: S.H.O., Writing: S.H.O., H.F.O.

Conflict of Interest: The author of this article (H.F.O.) are member of the Editorial Board of this journal. He was completely blind to the paper's peer-review process. Other author have nothing to disclose.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Starr MC, Boohaker L, Eldredge LC, et al. Acute Kidney Injury and Bronchopulmonary Dysplasia in Premature Neonates Born Less than 32 Weeks' Gestation. *Am J Perinatol*. 2020;37:341-8.
2. Askenazi D, Patil NR, Ambalavanan N, et al. Acute kidney injury is associated with bronchopulmonary dysplasia/mortality in premature infants. *Pediatr Nephrol*. 2015;30:1511-8.
3. Jetton JG, Boohaker LJ, Sethi SK, et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. *Lancet Child Adolesc Health*. 2017;1:184-94.
4. Koralkar R, Ambalavanan N, Levitan EB, McGwin G, Goldstein S, Askenazi D. Acute kidney injury reduces survival in very low birth weight infants. *Pediatr Res*. 2011;69:354-8.
5. Askenazi DJ, Feig DI, Graham NM, Hui-Stickle S, Goldstein SL. 3-5 year longitudinal follow-up of pediatric patients after acute renal failure. *Kidney Int*. 2006;69:184-9.
6. Grigoryev DN, Liu M, Hassoun HT, Cheadle C, Barnes KC, Rabb H. The local and systemic inflammatory transcriptome after acute kidney injury. *J Am Soc Nephrol*. 2008;19:547-58.
7. Dodd-o JM, Hristopoulos M, Scharfstein D, et al. Interactive effects of mechanical ventilation and kidney health on lung function in an in vivo mouse model. *Am J Physiol Lung Cell Mol Physiol*. 2009;296:L3-11.

8. Hassoun HT, Lie ML, Grigoryev DN, Liu M, Tudor RM, Rabb H. Kidney ischemia-reperfusion injury induces caspase-dependent pulmonary apoptosis. *Am J Physiol Renal Physiol*. 2009;297:F125-37.
9. Hoke TS, Douglas IS, Klein CL, et al. Acute renal failure after bilateral nephrectomy is associated with cytokine-mediated pulmonary injury. *J Am Soc Nephrol*. 2007;18:155-64.
10. Basu RK, Wheeler DS. Kidney-lung cross-talk and acute kidney injury. *Pediatr Nephrol*. 2013;28:2239-48.
11. Doi K, Ishizu T, Fujita T, Noiri E. Lung injury following acute kidney injury: kidney-lung crosstalk. *Clin Exp Nephrol*. 2011;15:464-70.
12. Husain-Syed F, Slutsky AS, Ronco C. Lung-Kidney Cross-Talk in the Critically Ill Patient. *Am J Respir Crit Care Med*. 2016;194:402-14.
13. Chen D, Jiang L, Li J, et al. Interaction of Acute Respiratory Failure and Acute Kidney Injury on in-Hospital Mortality of Patients with Acute Exacerbation COPD. *Int J Chron Obstruct Pulmon Dis*. 2021;16:3309-16.
14. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120:c179-84.
15. Higgins RD, Jobe AH, Koso-Thomas M, et al. Bronchopulmonary Dysplasia: Executive Summary of a Workshop. *J Pediatr*. 2018;197:300-8.
16. Li X, Yuan F, Zhou L. Organ Crosstalk in Acute Kidney Injury: Evidence and Mechanisms. *J Clin Med*. 2022;11:6637.
17. Starr MC, Schmicker RH, Halloran BA, et al. Premature infants born <28 weeks with acute kidney injury have increased bronchopulmonary dysplasia rates. *Pediatr Res*. 2023;94:676-82.
18. Askenazi DJ, Koralkar R, Hundley HE, Montesanti A, Patil N, Ambalavanan N. Fluid overload and mortality are associated with acute kidney injury in sick near-term/term neonate. *Pediatr Nephrol*. 2013;28:661-6.
19. Abosaif NY, Tolba YA, Heap M, Russell J, El Nahas AM. The outcome of acute renal failure in the intensive care unit according to RIFLE: model application, sensitivity, and predictability. *Am J Kidney Dis*. 2005;46:1038-48.
20. Hoste EA, Lameire NH, Vanholder RC, Benoit DD, Decruyenaere JM, Colardyn FA. Acute renal failure in patients with sepsis in a surgical ICU: predictive factors, incidence, comorbidity, and outcome. *J Am Soc Nephrol*. 2003;14:1022-30.
21. Neveu H, Kleinknecht D, Brivet F, Loirat P, Landais P. Prognostic factors in acute renal failure due to sepsis. Results of a prospective multicentre study. The French Study Group on Acute Renal Failure. *Nephrol Dial Transplant*. 1996;11:293-9.
22. Endre ZH. Renal ischemic preconditioning: finally some good news for prevention of acute kidney injury. *Kidney Int*. 2011;80:796-8.
23. Zimmerman RF, Ezeanuna PU, Kane JC, et al. Ischemic preconditioning at a remote site prevents acute kidney injury in patients following cardiac surgery. *Kidney Int*. 2011;80:861-7.
24. Venugopal V, Laing CM, Ludman A, Yellon DM, Hausenloy D. Effect of remote ischemic preconditioning on acute kidney injury in nondiabetic patients undergoing coronary artery bypass graft surgery: a secondary analysis of 2 small randomized trials. *Am J Kidney Dis*. 2010;56:1043-9.
25. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010;126:443-56.
26. Rocha G, Ribeiro O, Guimarães H. Fluid and electrolyte balance during the first week of life and risk of bronchopulmonary dysplasia in the preterm neonate. *Clinics (Sao Paulo)*. 2010;65:663-74.
27. Lorenz JM, Kleinman LI, Kotagal UR, Reller MD. Water balance in very low-birth-weight infants: relationship to water and sodium intake and effect on outcome. *J Pediatr*. 1982;101:423-32.
28. Bell EF, Warburton D, Stonestreet BS, Oh W. Effect of fluid administration on the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants. *N Engl J Med*. 1980;302:598-604.
29. Arikan AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. *Pediatr Crit Care Med*. 2012;13:253-8.
30. Santschi M, Juvet P, Leclerc F, et al. Acute lung injury in children: therapeutic practice and feasibility of international clinical trials. *Pediatr Crit Care Med*. 2010;11:681-9.
31. Oh W, Poindexter BB, Perritt R, et al. Association between fluid intake and weight loss during the first ten days of life and risk of bronchopulmonary dysplasia in extremely low birth weight infants. *J Pediatr*. 2005;147:786-90.
32. Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev*. 2014;2014:CD000503.
33. Domenech P, Perez T, Saldarini A, Uad P, Musso CG. Kidney-lung pathophysiological crosstalk: its characteristics and importance. *Int Urol Nephrol*. 2017;49:1211-5.
34. Joannidis M, Forni LG, Klein SJ, et al. Lung-kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup. *Intensive Care Med*. 2020;46:654-72.
35. Barakat MF, McDonald HI, Collier TJ, Smeeth L, Nitsch D, Quint JK. Acute kidney injury in stable COPD and at exacerbation. *Int J Chron Obstruct Pulmon Dis*. 2015;10:2067-77.
36. Chertow GM, Christiansen CL, Cleary PD, Munro C, Lazarus JM. Prognostic stratification in critically ill patients with acute renal failure requiring dialysis. *Arch Intern Med*. 1995;155:1505-11.
37. van den Akker JP, Egal M, Groeneveld AB. Invasive mechanical ventilation as a risk factor for acute kidney injury in the critically ill: a systematic review and meta-analysis. *Crit Care*. 2013;17:R98.
38. Li X, Hassoun HT, Santora R, Rabb H. Organ crosstalk: the role of the kidney. *Curr Opin Crit Care*. 2009;15:481-7.