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Acute kidney injury is associated with bronchopulmonary dysplasia/mortality in premature infants

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Abstract

Background—Acute kidney injury (AKI) impairs electrolyte balance, alters fluid homeostasis and decreases toxin excretion. More recent data suggest it also affects the physiology of distant organs.

Methods—We performed a prospective cohort study which involved 122 premature infants [birth weight (BW) 1200 g and/or gestational age (GA) <31 weeks] to determine relationships between AKI and bronchopulmonary dysplasia (BPD)/mortality. Days until oxygen discontinuation was compared between those with and without AKI in survivors who received oxygen for ≥24 h.

Results—Acute kidney disease, defined by a rise in serum creatinine (SCr) of ≥0.3 mg/dl or an increase in SCr of ≥150 %, occurred in 36/122 (30 %) of the premature infants. Those with AKI had a 70 % higher risk of oxygen requirement or of dying at 28 days of life [relative risk (RR) 1.71, 95 % confidence interval (CI) 1.22–2.39; $p < 0.002$]. This association remained after controlling for GA, pre-eclampsia, 5 min Apgar score and percentage maximum weight change (max % weight) in the first 4 days (RR 1.45, 95 % CI 1.07–1.97; $p < 0.02$). Similar findings were noted for receipt of mechanical ventilation/death by day 28 (adjusted RR 1.53, 95 % CI 1.05–2.22; $p < 0.03$). Those without AKI were 2.5-fold more likely to come off oxygen [hazard ratio (HR) 1.3–5; $p < 0.02$] than those with AKI, even when controlling for GA, pre-eclampsia, 5 min Apgar and max % weight (multivariate HR 2.0, 95 % CI 0.9–4.0; $p < 0.06$).

Conclusions—In premature infants, AKI is associated with BPD/mortality. As AKI could lead to altered lung physiology, interventions to ameliorate AKI could improve long-term BPD.

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Potential conflicts of interest None.

Keywords

Acute renal failure; Acute lung injury; Chronic lung disease; Organ crosstalk; Neonate

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Introduction

Acute kidney injury (AKI), previously referred to as acute renal failure, is common in premature infants, with incidence rates estimated at between 12.5 and 18 % [1–3]. Past research has reported that premature infants with AKI have higher mortality even when controlling for important confounders [4, 5], an association that has been observed in both pediatric and adult critically ill populations.

Premature infants often develop bronchopulmonary dysplasia (BPD), a form of neonatal chronic lung disease that usually develops in this infant population following respiratory distress syndrome. The etiology of BPD is complex and includes the underlying lung immaturity, with superimposed effects of infection, fluid overload and trauma from mechanical ventilation. Regardless of the etiologic pathway, persistent inflammation leads to abnormal lung development and progressive lung dysfunction with varying magnitude of fibrosis and pulmonary hypertension [6–10]. BPD is one of the most important co-morbidities in premature neonates as it is associated with high mortality in the first years of life, a lifetime of risk for persistent pulmonary impaired function [11] and high medical expenditures [6, 12].

Over the last few decades, there is growing appreciation that AKI is a systemic disease that can affect distant organs and consequently impact overall critical illness. Although the precise molecular mechanisms are not fully understood [13], animal models have provided evidence for a deleterious impact of bidirectional kidney–lung injury [14–17]. For example, in 2008 Grigory et al. showed that after ischemic AKI, mice had an inflammatory response in the lung which paralleled that found in the kidney [14]. It is important to note that these animal models of kidney injury do not affect volume status, which highlights that non-oliguric AKI leads to abnormal lung function and architecture. Adult critically ill patients with both AKI and acute lung injury (ALI) have mortality rates of >80 %, which are significantly worse than those of adult patients with only lung or kidney injury [18, 19]. In children, a clear association exists between AKI and lung outcomes, including poor lung function and higher number of days on a ventilator [20, 21]. The association between AKI and lung disease has been only briefly mentioned in the neonatal literature. In 2005, Oh et al. reported the association between fluid intake and weight loss during the first 10 days of life and the risk of BPD in extremely low birth weight infants [22]. In 2010, Rocha et al. showed an association between fluid and electrolyte balance in the first week of life and the risk of BPD in preterm neonates [23].

In order to better understand the association between AKI and lung disease in premature infants, we performed a prospective cohort study on 122 premature infants. Our primary hypothesis was that AKI would be associated with BPD/mortality independent of important potential confounders. We evaluated BPD and mortality as a composite outcome as they are competing outcome variables. We assessed both the use of oxygen and the use of ventilator

at two different time points [28 days of life and 36 weeks post-menstrual age (PMA)]. Our secondary hypothesis was that AKI is associated with a longer duration of oxygen supplementation after adjustment for potential confounders in those who survived to 28 days of life.

Methods

Study population

This prospective cohort study was conducted in the Regional Neonate Intensive Care Unit (NICU) located on the University of Alabama at Birmingham (UAB) campus between February 2012 and June 2013. The study population consisted of 122 infants with a birth weight (BW) of ≥ 1200 g and/or gestational age (GA) of ≥ 31 weeks. Infants were excluded if they had a known congenital abnormality of the kidney or urinary tract. We followed enrolled infants from the time of birth until 36 weeks PMA or hospital discharge, whichever occurred first. Parental informed consent was obtained from parents or guardians. UAB's Institutional Review Board approved the study.

Variable definitions

The neonatal AKI definition used was modified from the KDIGO as previously described by Jetton et al. (Table 1) [24]. For this study, we did not include urine output criteria because it is often difficult to measure urine output in premature infants, and non-oliguric AKI is very common in this population. Since serum creatinine (SCr) decreases in neonates after birth dependent on GA, the baseline SCr level was defined as the lowest previous SCr value. Stage 1 AKI was defined as a rise in SCr level of at least 0.3 mg/dl from the baseline value or an increase in SCr by 150–200 %, stage 2 AKI was defined as a 200–300 % increase in SCr level and stage 3 AKI was defined if there was an increase in SCr level of ≥ 300 % or the SCr value was ≥ 2.5 mg/dl. SCr was measured on days 1, 2, 3, 4 and 12 for most infants in addition to any clinically measured values. A median of five (range 2–14) SCr values were obtained for each patient during the first 2 weeks of life. We defined percentage weight change (% wt) as: $(\text{current weight} - \text{BW})/\text{BW}$; the maximum percentage weight change (max % wt) was used as a surrogate for fluid status.

To define BPD, we evaluated the requirement of supplemental oxygen and the requirement of positive pressure ventilation separately. We explored the receipts of these two interventions at two time points (28 days of age, and 36 weeks PMA). BPD was considered to be moderate if the fraction of inspired oxygen (FiO_2) requirement was ≥ 30 %, and to be severe if the infant had a >30 % FiO_2 requirement or positive pressure ventilation [10]. We evaluated mortality at both of these time points in accordance with current research trends to define mortality in premature infants. We chose the composite outcome of BPD/mortality as our primary outcome because these are competing outcomes and deemed this composite outcome to be necessary as follows: if one was only to consider BPD as an outcome, and an infant died at 27 days, then the infant would be considered as not having BPD (and would appear to have a good outcome) when in fact, death was the outcome. Finally, we calculated the number of days until oxygen discontinuation in those who received oxygen for at least 24 h and survived to 28 days of life.

Statistical analysis

Descriptive statistics were performed to determine differences between infants with and without AKI. A p value of <0.05 was considered to be statistically significant. Normally distributed continuous variables were compared using Student's t test, and non-normally distributed variables were analyzed using the Mann–Whitney U test. The Cochran–Mantel–Haenszel chi square test or Fisher's exact test were used where appropriate.

A modified Poisson regression model with a robust variance was performed to provide risk ratio (RR) estimates of AKI on BPD/mortality while controlling for known and measured confounding variables, as previously described [25, 26]. Because the number of events (BPD/deaths) for the selected outcomes varied between 33 and 60, we chose six variables (according to the general rule of 1 variable for 10 events) a priori to control for demographics, severity of illness and co-morbidities. The chosen variables were GA, BW, maternal pre-eclampsia, 5 min Apgar, positive blood culture and max % wt as these have been previously shown to be associated with AKI and BPD. The final models were selected using stepwise backward selection to include variables with a p value of <0.2 .

In addition to the assessment of AKI on the risk of BPD/mortality, a Cox proportional hazard model was used to estimate hazard ratios (HR) and associated 95 % confidence intervals (CI) for the association between AKI and time to removal from oxygen among neonates exposed to oxygen who survived through to day 28 of life. Two-sided p values with $p < 0.05$ were considered to be statistically significant. SAS version 9.3 (SAS Institute Inc., Cary, NC) was used for all statistical analyses.

Results

Of the 281 infants who met the inclusion criteria, we included 122 (43 %) in the study. Reasons for non-inclusion were refusal of consent ($n = 75$); not available ($n = 76$); transferred from other hospitals ($n = 8$). No significant differences were detected between enrolled and non-enrolled infants with regards to BW, GA and 5 min Apgar scores (Fig. 1).

Cumulative incidence of AKI by day 15 of life was 36/122 (30 %) (31 infants had stage 1 AKI, 2 had stage 2 AKI, 3 had stage 3 AKI). By the 15th day of life, compared to infants without AKI, those with AKI had a lower BW (mean 879 ± 349 vs. 1002 ± 301 g; $p = 0.05$) and younger GA (mean 26.3 ± 2.3 vs. 27.5 ± 2.1 weeks; $p = 0.003$) and were more likely to have culture-positive infections (33 vs. 10 %; $p = 0.002$) and to receive umbilical arterial catheterization (58 vs. 35 %; $p = 0.01$) (Table 2). Infants with AKI were less likely than infants without AKI to have a mother with pre-eclampsia (8 vs. 37 %; $p = 0.001$). Infants with AKI had a lower number of oxygen-free days within the first 28 days of life and higher max % wt in the first 4 days. At 36 weeks PMA, infants with AKI were more likely to have severe BPD or to have died ($p < 0.04$).

Infants with AKI were more likely to have the composite outcomes of oxygen support/death and mechanical ventilation/death at both 28 days of life and 36 weeks PMA (all $p < 0.05$). For example, those with AKI had higher rates of oxygen requirement/death at 28 days of life than those without AKI [25/36 (69 %) vs. 35/86 (41 %); $p < 0.01$] (Table 3).

Those with AKI had a 70 % higher risk of an oxygen requirement/death at 28 days (RR 1.71, 95 % CI 1.22–2.39; $p < 0.002$) (Table 4). This association remained after controlling for GA, pre-eclampsia, 5 min Apgar score and max % wt (RR 1.45, 95 % CI 1.07–1.97; $p < 0.02$) (Table 4). Similarly, after controlling for GA, pre-eclampsia, 5 min Apgar score, positive blood cultures and % wt, those infants with AKI had a 60 % increased risk of needing mechanical ventilation or dying by day 28 (RR 1.53, 95 % CI 1.05–2.22; $p < 0.03$) (Table 5).

Infants with AKI had an increased RR to receive oxygen support/death and mechanical ventilation/death at 36 weeks PMA and showed a trend towards higher RR in the multivariate analysis, similar to the 28-day analysis. However, the multivariate analysis for BPD at 36 weeks PMA did not show a statistically significant finding, with p values of 0.14 and 0.2, respectively (Tables 4, 5).

In those infants who received oxygen on the first day of life and survived to 36 weeks PMA, those without AKI were 2.5-fold more likely to come off oxygen (univariate HR 1.3–5; $p < 0.02$). After controlling for birth weight, pre-eclampsia and 5 min Apgar score, those without AKI continued to have a twofold higher chance of coming off oxygen than those who had AKI (HR 2.0, 95 % CI 0.9–4.0; $p = 0.06$) (Table 6).

Discussion

The results of our study suggest an association between kidney injury and lung diseases/mortality in critically ill premature infants. Even after controlling for known potential confounders, those infants with AKI were more likely to receive respiratory support and/or to die at 28 days of life. In addition, AKI was independently associated with longer oxygen need/exposure. These findings support previous studies done in animals and adults which showed an association between AKI and acute liver injury [13, 14, 18, 19].

We were also able to show that AKI was *independently* associated with oxygenation/death and ventilator/death at 28 days of life, but not at 36 weeks PMA. Because the crude RR were similar between both time points, it is likely that if we had a larger sample size we would have been able to show independent associations at 36 weeks PMA. Further studies using larger sample sizes are needed to explore these associations.

The bidirectional crosstalk between kidney and lung has been clearly documented in multiple animal models. For example, in 2007, Hoke et al. [17] showed pulmonary injury independent of renal ischemia and highlighted the critical role of the kidney in the maintenance of serum cytokine balance and pulmonary homeostasis. Dodd et al. [15] showed a complex interaction between mechanical ventilation and AKI in which the sensitivity of the lung to trauma varies with the magnitude of the trauma and may involve a modification of pulmonary neutrophil activity by AKI. Hassoun et al. [16] identified 66 apoptosis-related genes prominently upregulated in the mouse lung after ischemic AKI. These and other studies suggest that the kidney serves a critical role in maintaining systemic cytokine balance and that kidney ischemia alters systemic inflammation and leads to an inflammatory response in the lung and other organs. Similar findings have been observed in

other critically ill populations. Arikan et al. [20] found that those critically ill children with AKI had a higher oxygenation index at different time points in their critical illness. Valentine et al. [21] showed that in children who required ventilator support, those with AKI had a decreased number of ventilator-free days.

We also noted an association in the maximum % wt within the first 4 days of life and BPD/mortality outcomes. Others have noted a similar effect of fluid provision and clinical outcomes, but have used different surrogate markers of fluid homeostasis [22, 23]. Because fluid provision is a potentially modifiable risk factor and there is wide clinical practice variance on the amount of fluid prescribed to premature infants, this observation needs to be further explored.

Incidentally it was observed that infants whose mothers had pre-eclampsia were less likely to have AKI (8 vs. 37 %; $p = 0.001$). Future studies with larger sample sizes are needed to perform more robust risk factor analysis of this important association. There are a number of possible reasons for this association. First, pre-eclampsia could lead to intermittent ischemic pre-conditioning; animal and human studies suggest that an ischemic insult with recovery minimizes the effect of ischemia a few days later. Second, this association may represent differences in subjects whereby the indication (i.e. pre-eclampsia vs. fetal distress) for early delivery may differ. Third, it is possible that those infants whose mothers had pre-eclampsia had been given dexamethasone or other interventions which prevented AKI in the infant. Further work will be necessary to enhance our understanding of this association.

To our knowledge, this is the first prospective cohort study looking at the incidence and association between AKI and BPD/mortality in premature infants. We use contemporary definitions of both AKI (using prospectively collected SCr values) and BPD. Since all infants were enrolled in a consecutive time frame and were treated in the same NICU, we can assume consistency over the quality of medical care received. There were no significant differences in BW, GA and 5 min Apgar scores between consenting and non-consenting infants, thus allowing for generalizability to the entire populations cared for at our institution during this time frame. Despite the strengths of this study, we acknowledge several important limitations. We used changes in SCr as criteria to diagnose AKI. We acknowledge that this definition has not been rigorously tested against other AKI definitions of premature neonates. However, at a recent NIH workshop on neonatal AKI, a panel of experts concluded that at this point in time, this definition currently provides the best assessment of neonatal AKI. Our study design allowed us to reliably determine whether an infant had AKI during the first 2 weeks of life, but we cannot be certain that infants developed AKI after 2 weeks of life. Due to the study design, AKI status by urine output criteria was not possible. It is possible that different definitions of AKI (which incorporate urine output and fluid status) could affect the association between AKI and BPD. Similarly, we acknowledge that the definition of BPD and the quantity of support needed may be an imprecise method to quantify true long-term lung disease. As mortality and BPD are competing outcomes, our analysis focused on composite outcomes of BPD/death, and we acknowledge the limitations of this approach. Our analysis that those without AKI were more likely to come off oxygen, independent of confounders, suggests that our findings indeed point to the association between lung and kidney injury. Finally, although we attempted to control for important

demographic and clinical variables known to be associated with both BPD and AKI, we acknowledge that unknown/unmeasured variables could account for these associations. Larger multi-center studies in neonates will be needed to validate and generalize our findings.

In conclusion, we show that AKI is independently associated with BPD/death in premature infants. Because chronic lung disease accounts for higher morbidity, mortality and medical cost in this population, strategies to prevent/ameliorate the impact of AKI could lead to improved lung outcomes. Further work is greatly needed to explore mechanisms of the bidirectional nature of kidney and lung organ crosstalk in premature animal models, as a fuller understanding of these mechanism could lead to targeted interventions that may impact the morbidity and mortality ascribed to lung and kidney damage. These insights will improve our understanding of how the kidney and lung interacts during times of stress.

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Fig. 1.

Breakdown of the eligible, enrolled and non-enrolled infants in the study. *VLBW* Very low birth weight, *GA* gestational age

Table 1

Classification of acute kidney injury using the Kidney Disease: Improving Global Outcomes serum creatinine criteria

Acute kidney injury stage	Serum creatinine
Stage 1	SCr increase of 0.3 mg/dl from lowest previous value OR SCr increase of 150–200 % from lowest previous value
Stage 2	SCr increase of >200–300 % from lowest previous value
Stage 3	SCr value of 2.5 mg/dl OR SCr increase of >300 % from lowest previous value

Baseline serum creatinine (SCr) was defined as the lowest previous SCr value because SCr decreases in neonates after birth, dependent on gestational age

Table 2

Demographics differences between infants with and without acute kidney injury by day 15 of life

Infant characteristics	AKI (N = 36)	No AKI (N = 86)	p value ^a
Sex (male)	15 (42 %)	47 (55 %)	0.1
Race			0.1
Black	20 (56 %)	47 (55 %)	
White	16 (44 %)	31 (36 %)	
Hispanic	0 (0 %)	8 (9 %)	
Gestational age (weeks)	26.3±2.3	27.5±2.1	0.003
Birth weight (g)	879±349	1002±301	0.05
1-Min Apgar (score)	3±2	4±2	0.5
5-Min Apgar (score)	6±1	6±1	0.2
Maximum % weight change (days 1–4)	−9.4±13.6	−7.4±11.7	0.05
Umbilical arterial catheterization	21 (58 %)	30 (35 %)	0.01
Surfactant administration	22 (61 %)	43 (50 %)	0.3
Indocin administration	19 (53 %)	30 (35 %)	0.06
Oxygen-free days within the first 28 days	15.8±12.7	22.7±9.5	0.002
Positive blood culture day 15	12 (33 %)	9 (10 %)	0.002
Outcome			
No, mild or moderate BPD	20 (56 %)	67 (78 %)	<0.04
Severe BPD	8 (22 %)	12 (14 %)	
Died	8 (22 %)	7 (8 %)	
Days until death in those that died (N = 13)	13.3±8.0	12.3±8.4	0.8
Maternal characteristics (N)			
Prenatal care	33 (92 %)	80 (93 %)	0.7
Diabetes	3 (8 %)	9 (10 %)	0.7
High blood pressure	11 (31 %)	24 (28 %)	0.7
Antenatal steroids	34 (94 %)	84 (98 %)	0.3
Antenatal indomethacin	6 (17 %)	7 (8 %)	0.1
Smoking	5 (14 %)	12 (14 %)	0.9
Pre-eclampsia	3 (8 %)	32 (37 %)	0.001
Pregnancy outcome multiple birth	14 (39 %)	22 (26 %)	0.1
History of drug abuse	3 (8 %)	5 (6 %)	0.6
Chorioamnionitis	18 (50 %)	37 (43 %)	0.4

Data in table are presented as the number with the percentage in parenthesis, or as the mean ± standard deviation (SD)

AKI, Acute kidney injury; BPD, bronchopulmonary dysplasia

^aThe p value for all variables was estimated using the chi-square or t-test for categorical and continuous variables, respectively, with the exception of Maximum % weight change (days 1–4), which was estimated using the Wilcoxon test

Table 3

Association between acute kidney injury and degree of bronchopulmonary dysplasia/mortality

Oxygen support/death and mechanical ventilation/death	AKI		<i>p</i> value
	Yes (<i>N</i> = 36)	No (<i>N</i> = 86)	
Oxygen support or death			
At 28 days of Life	25 (69 %)	35 (41 %)	<0.01
At 36 weeks PMA	19 (53 %)	26 (30 %)	<0.02
Mechanical ventilation or death			
At 28 days of Life	20 (56 %)	23 (27 %)	<0.01
At 36 weeks PMA	12 (33 %)	11 (13 %)	<0.01

Data in table are presented as the number of patients with the percentage in parenthesis AKI, Acute kidney injury; PMA, Post menstrual age

Table 4

Risk ratios and associated 95 % confidence intervals for the association between oxygen support or death and characteristics of interest^a

Infant characteristics	Crude RR (95 % CI)	<i>p</i> value	Adjusted RR (95 % CI)	<i>p</i> value
28 days of life				
Gestational age (1 week)	0.76 (0.71–0.82)	<0.0001	0.81 (0.75–0.88)	<0.0001
Birth weight (100 g)	0.79 (0.72–0.86)	<0.0001		
Pre-eclampsia	1.34 (0.94–1.91)	0.11	1.85 (1.27–2.71)	<0.002
5 min Apgar	0.83 (0.79–0.88)	<0.0001	0.91 (0.85–0.98)	<0.02
Positive blood culture in first 2 weeks	2.06 (1.54–2.75)	<0.0001	1.21 (0.91–1.62)	0.19
Maximum % weight change (days 1–4)	1.02 (1.01–1.03)	<0.0001	1.01 (0.99–1.02)	0.16
AKI by day 15	1.71 (1.22–2.39)	<0.002	1.45 (1.07–1.97)	<0.02
36 weeks post-menstrual age				
Gestational age (1 week)	0.75 (0.68–0.82)	<0.0001		
Birth weight (100 g)	0.77 (0.68–0.87)	<0.0001	0.84 (0.74–0.96)	<0.01
Pre-eclampsia	1.37 (0.86–2.19)	0.19	1.54 (0.88–2.67)	0.13
5 min Apgar	0.78 (0.74–0.84)	<0.0001	0.84 (0.76–0.92)	<0.0001
Positive blood culture in first 2 weeks	2.41 (1.61–3.60)	<0.0001	1.46 (0.94–2.25)	0.09
Maximum % weight change (days 1–4)	1.03 (1.02–1.04)	<0.0001	1.01 (.99–1.03)	0.26
AKI by day 15	1.75 (1.12–2.73)	<0.02	1.44 (0.89–2.33)	0.14

RR, Risk ratio; CI, confidence interval; AKI, Acute kidney injury

^aBased on the modified Poisson regression with robust variance

Table 5

Risk ratios (RR) and associated 95 % confidence intervals for the association between mechanical ventilation or death and characteristics of interest^a

Infant characteristics	Crude RR (95 % CI)	<i>p</i> value	Adjusted RR (95 % CI)	<i>p</i> value
28 days of life				
Gestational age (1 week)	0.68 (0.61–0.75)	<0.0001	0.76 (0.68–0.84)	<0.0001
Birth weight (100 g)	0.75 (0.66–0.86)	<0.0001		
Pre-eclampsia	1.08 (0.64–1.81)	0.8	1.86 (1.12–3.07)	0.02
5 min Apgar	0.75 (0.70–0.81)	<0.0001	0.84 (0.77–0.93)	<0.0004
Positive blood culture in first 2 weeks	3.15 (2.13–4.65)	<0.0001	1.69 (1.16–2.46)	<0.007
Maximum % weight change (days 1–4)	1.03 (1.02, 1.05)	<0.0001	1.02 (0.99–1.03)	0.06
AKI by day 15	2.08 (1.32–3.28)	<0.002	1.53 (1.05–2.22)	0.03
36 weeks post-menstrual age				
Gestational age (1 week)	0.59 (0.50–0.70)	<0.0001	0.61 (0.50–0.73)	<0.0001
Birth weight (100 g)	0.68 (0.56–0.82)	<0.0001		
Pre-eclampsia	0.69 (0.28–1.72)	0.43		
5 min Apgar	0.73 (0.64–0.83)	<0.0001		
Positive blood culture in first 2 weeks	3.09 (1.55–6.18)	<0.002		
Maximum % weight change (days 1–4)	1.04 (1.01–1.06)	<0.002	1.03 (1.00–1.05)	0.02
AKI by day 15	2.61 (1.27–5.35)	<0.01	1.54 (0.80–2.97)	0.20

^aBased on the modified Poisson regression with robust variance

AKI, Acute kidney injury

Table 6

Hazard ratios (HR) and associated 95 % confidence intervals for the association between characteristics of interest and time to removal from oxygen by day 28^a

Infant characteristics	Crude HR (95 % CI)	<i>p</i> value	Adjusted HR (95 % CI)	<i>p</i> value
Gestational age (1 week)	1.6 (1.4–1.9)	<0.0001	1.6 (1.3–1.9)	<0.0001
Birth weight (100 g)	1.2 (1.1–1.3)	<0.0001		
Pre-eclampsia	0.6 (0.3–1.1)	0.13	0.4 (0.2–0.8)	<0.008
5 min Apgar	1.7 (1.3–2.2)	<0.0002	1.2 (0.9–1.6)	0.10
Positive blood culture in first 2 weeks	0.15 (0.04–0.6)	<0.01		
Maximum % weight change (days 1–4)	0.97 (0.9–0.99)	<0.02	0.98 (.9–1.01)	0.18
NO AKI	2.5 (1.3–5.0)	<0.02	2.0 (0.9–4.0)	0.06

^aHazard ratio (95 % confidence interval) based on the Cox proportional hazard model

AKI, Acute kidney injury