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Conflict of Interest

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Acute Kidney Injury is Associated with Poor Lung Outcomes in Infants Born ≥32 Weeks of Gestational Age

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Abstract

Objective—This study aimed to evaluate the association between acute kidney injury (AKI) and lung outcomes in infants born ≥32 weeks of gestational age (GA).

Study Design—Secondary analysis of infants ≥32 weeks of GA in the assessment of worldwide acute kidney injury epidemiology in neonates (AWAKEN) retrospective cohort (n = 1,348). We used logistic regression to assess association between AKI and a composite outcome of chronic lung disease (CLD) or death at 28 days of age and linear regression to evaluate association between AKI and duration of respiratory support.

Results—CLD occurred in 82/1,348 (6.1%) infants, while death occurred in 22/1,348 (1.6%); the composite of CLD/death occurred in 104/1,348 (7.7%). Infants with AKI had an almost five-fold increased odds of CLD/death, which remained after controlling for GA, maternal polyhydramnios, multiple gestations, 5-minute Apgar's score, intubation, and hypoxic–ischemic encephalopathy (adjusted odds ratio [OR] = 4.9, 95% confidence interval [CI]: 3.2–7.4; $p < 0.0001$). Infants with AKI required longer duration of respiratory support (count ratio = 1.59, 95% CI: 1.14–2.23, $p = 0.003$) and oxygen (count ratio = 1.43, 95% CI: 1.22–1.68, $p < 0.0001$) compared with those without AKI.

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Conclusion—AKI is associated with CLD/death and longer duration of respiratory support in infants born at ≥32 weeks of GA. Further prospective studies are needed to elucidate the pathophysiologic relationship.

Keywords

acute kidney injury; acute renal failure; acute lung injury; chronic lung disease; organ crosstalk; neonate

Chronic lung disease (CLD) is the most prevalent chronic illness in infants, diagnosed in approximately 14,000 neo-nates born in the United States each year.[1] Although CLD more frequently affects premature infants, it also occurs in those born at older gestational ages. While infants born ≥32 weeks have historically been considered low risk for subsequent respiratory complications, recent studies show that they may have respiratory vulnerabilities similar to that of very prematurely born neonates.[2,3] This increased risk is thought to be due to deficient lung volume and impaired alveolar maturation, resulting in incomplete lung development and altered lung function that persists into child- hood.[4,5] Management of CLD takes a toll on the health care system. with initial hospitalization expenses of over $400,000 per diagnosis, readmission rate of 50% within the first year, and an overall cost of $2.4 billion, an amount second only to the costs associated with the treatment of pediatric asthma.[6,7]

Acute kidney injury (AKI) is common in pediatric patients, occurring in critically-ill children of all ages.[8] AKI occurs in up to 30% of infants ≥32 weeks of gestation hospitalized in the neonatal intensive care unit (NICU).[9] There are growing data suggesting that AKI is a systemic disease that affects the physiology of distant organs, including the lung.[10] While the molecular mechanisms remain unclear, there appears to be a bidirectional relationship between the kidney and lung in acute illness.11 In both adults and children, AKI is associated with poor short and long-term pulmonary outcomes as critically ill pediatric and adults patients with both AKI and lung injury have higher mortality rates and increased odds of prolonged mechanical ventilation than those with either lung or kidney injury alone.[12,13]

Few studies have explored the association between AKI and lung disease in later preterm and term infants.[14] To address this knowledge gap, we analyzed the database from a large multicenter observational cohort of infants admitted to 24 participating neonatal intensive care units in 4 different countries.[14] We hypothesized that compared with those without AKI, neonates with AKI would have higher adjusted rates of the composite outcome (CLD or death) and longer durations of respiratory support.

Materials and Methods

Study Design and Participants

The Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study is a multicenter, multi- national retrospective observational cohort of infants admitted to the NICU between January 1 and March 31, 2014 from 24 institutions in four countries. A complete description of the development of the AWAKEN database and the epidemiology of neonatal AKI have been published elsewhere.[9,15] The AWAKEN cohort included infants

admitted during the study period receiving intravenous fluids for at least 48 hours after admission. Infants were excluded from the AWAKEN study if they were admitted after 14 days of age, had congenital heart disease requiring surgical repair within 7 days, lethal chromosomal anomaly, died within 48 hours of NICU admission, or had severe congenital kidney, or urinary tract abnormalities. For this analysis, we chose to only study those neonates ≥32 weeks of gestation as the pathophysiology and definition of CLD is different than those <32 weeks of GA.[9,15] Infants were excluded if serum creatinine or urine output data sufficient to determine AKI status were not available. Information on AKI status acquired as part of clinical care was obtained, including urine output for the first week of life, and serum creatinine data throughout hospitalization. Additionally, because the pathophysiology of lung disease may be unique in those with severe congenital heart disease, severe congenital kidney disease (including those with vesicoureteral reflux grades 4 to 5, moderate or severe hydronephrosis, bilateral hypoplasia, dysplasia or renal agenesis, and autosomal recessive polycystic kidney disease), and abdominal wall defects, those infants were excluded.[9] The Institutional Review Board (IRB) at the University of Alabama in Birmingham approved this collaborative study, and each center received approval from their respective IRBs for participation. The study design allowed for a waiver of informed consent or parental permission. This study is registered with ClinicalTrials.org, number NCT02443389.

Definitions

The exposure of interest was AKI within the first 28 days of age; therefore, the AKI diagnosis was prior to determination of CLD. Neonatal AKI was defined using the modified Kidney Disease Improving Global Outcomes (KDIGO) definition.[16,17] AKI was defined by a rise in serum creatinine of ≥0.3 mg/dL within 48 hours or an increase of >150% from previous lowest value or a urine output of <1 mL/kg/h during a 24-hour period on postnatal days 2 to 7 of age (►Supplementary Table S1, available in the online version).[18] We deemed data insufficient for classification of serum creatinine defined AKI and urinary output defined AKI if an infant had less than two serum creatinine measurements assessed during the first 28 days or if an infant did not have at least 1 day with quantifiable urinary output on days 2 to 7, respectively. The maximum AKI severity was classified into one of three stages based on KDIGO definitions using the highest stage based on either serum creatinine or urinary output criteria (►Supplementary Table S1, available in the online version).[19] We defined severe AKI as stage 2 or 3 AKI because these stages have been associated with increased mortality in studies involving children.[20,21]

The primary outcome of interest was diagnosis of CLD or death at 28 days of age. We used the standardized National Institute of Child Health and Human Development (NICHD) definition of CLD for those ≥32 weeks which used a requirement of supplemental oxygen at 28 postnatal days to define CLD (►Supplementary Table S2, available in the online version).[1] Severity of CLD was determined by consensus definitions at 56 days of age or discharge, whichever came first, and was considered mild if the infant required no respiratory support at 56 days, moderate if the fraction of inspired oxygen (FiO_2) was <0.30 and severe if the infant required ≥0.30 or positive pressure ventilation.[1] Oxygen challenge testing was not performed routinely given the retrospective nature of the study and was not

considered as part of the definition of CLD. We chose a composite outcome of CLD/death as our primary outcome because these are competing outcomes and it is commonly used in this patient population.[14,22]

To determine duration of respiratory support and/or supplemental oxygen dependence, we evaluated oxygen and mechanical ventilation requirement on 7-day age and weekly thereafter for 4 weeks. We considered ventilatory respiratory support as either noninvasive positive pressure support (including all modalities of continuous positive airway pressure and high-flow nasal canulae) or invasive mechanical ventilation (including all modalities of respiratory support provided by endotracheal tube, including but not limited to conventional mechanical ventilation, oscillatory ventilation, and jet ventilation).

Statistical Analysis

We used descriptive statistics to determine differences between infants with and without CLD/death. Categorical variables were analyzed by proportional differences with either Chi-square or Fisher's exact tests. For normally distributed continuous variables, the means and Standard Deviations (SD) were reported and analyzed using the Student's *t*-test. For nonnormally distributed variables, medians, and interquartile range (IQR) were reported and groups compared with the Wilcoxon's rank-sum test.

For the comparison of AKI incidence overall, AKI by stage, and type of AKI, an unconditional logistic regression, ordinal logistic regression, and multinomial logistic regression were used, respectively, to estimate odds ratios (ORs) and 95% confidence intervals (CIs). We used a backward selection approach (with a significance level < 0.1 needed to remain in the model) to construct logistic regression models to estimate ORs for the adjusted association between AKI and our primary outcome (CLD/death). To determine the adjusted association between AKI and weeks of ventilator and oxygen dependence, two analyses were conducted: first, a row means score differ Cochran–Mantel–Haenszel statistic was used to compare the distribution of weeks of ventilator dependence, oxygen dependence, and FiO_2 levels; second, in a multivariable analysis we used a zero-inflated Poisson's analysis. This analysis combines a logistic process to determine the factors that affect whether or not an infant required mechanical ventilation and a Poisson's process to determine the factors that impacted the count of weeks a subject was on a ventilator.[23] For all analyses, a two-sided *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (Statistical Analysis Software Institute Inc., Cary, NC).

Results

Population

Of the 2,189 infants in the AWAKEN cohort, 295 were removed from the analysis for having at least one of the following exclusions: abdominal wall defects, severe congenital renal abnormalities, congenital heart disease, or insufficient serum creatinine measurements, and/or no urine output data (►Fig. 1). Of the remaining 1,894 infants, 1,348 (71.2%) were ≥32 weeks of GA and made up the final cohort for this analysis. Slightly more infants in the

cohort were male (56.0%), and the majority identified as non- Hispanic ethnicity (70.5%), and white race (57.6%). The mean gestational age of the cohort was 36.1 ± 2.7 weeks and the mean birth weight was 2,660 T 820 g.

Demographic Differences between those with CLD/Death versus those without CLD/Death

CLD occurred in 82 (6.1%) infants while death occurred in 22 (1.6%) infants; thus, the composite of CLD/death occurred in 104 (7.7%) of infants (►Table 1). Infants with CLD/death had lower median 1-minute Apgar's scores (5 vs. 8, $p < 0.0001$) and lower 5-minute Apgar's scores (8 vs. 9, $p < 0.0001$). Maternal polyhydramnios occurred more frequently in infants with CLD/death compared with those who did not develop CLD or die (11.5 vs. 3.7%, $p = 0.0005$). Approximately 50% of infants with CLD/death were intubated as part of initial resuscitation, compared with 14% of those without CLD/death ($p < 0.0001$). There were no significant differences in gender, race, ethnicity, gestational age, birthweight, or maternal corticosteroid administration between groups.

AKI Rates and Association with CLD/Death

AKI occurred in 362 (26.9%) of infants. Of those infants with AKI, 171 (47.2%) had stage-1 AKI, 77 (21.3%) had stage-2 AKI, and 114 (31.5%) had stage-3 AKI. A total of 191 (52.8%) had severe (stage 2 or 3) AKI (►Table 2). Among infants with AKI, diagnosis was based on serum creatinine alone in 122 (33.7%), urine output alone in 201 (55.6%), and on both serum creatinine and urine output in 39 (10.8%).

Compared with those with no CLD, AKI occurred more frequently in those with mild/moderate CLD (OR = 4.54, 95% CI: 2.62–7.84) or severe CLD/death (OR = 5.27, 95% CI: 2.90–−9.59; ►Table 2). These associations were similar in ordinal logistic models. Among those diagnosed with AKI and mild/moderate CLD, AKI was more likely to be diagnosed by serum creatinine alone (OR = 5.71, 95% CI: 2.31–14.08) or serum creatinine and urine output combined (OR ¼ 7.12, 95% CI: 2.31–21.92). A similar but weaker pattern was observed for those with severe CLD/death for AKI diagnosed by serum creatinine alone (OR = 3.50, 95% CI: 1.48–8.32) or both serum creatinine and urine output (OR = 4.74, 95% CI: 1.56–14.42).

Infants with AKI had a near five-fold increased odds of CLD/death (unadjusted OR = 4.89, 95% CI: 3.21–7.35). This association remained after controlling for GA, 5-minute Apgar's score, intubation during initial resuscitation, maternal polyhydramnios, multiple gestations, and admission for hypoxic–ischemic encephalopathy (OR = 4.57, 95% CI: 2.97–7.17). GA (OR = 0.88, 95% CI: 0.81–0.96) and intubation as part of resuscitation (OR = 4.88, 95% CI: 3.12–7.61) were also significantly associated with CLD/death after multivariable adjustment (►Table 3).

Association between AKI and Number of Weeks of Respiratory Support

Infants with AKI more frequently required longer duration of invasive and noninvasive respiratory support within the first 4 weeks of life compared with infants without AKI ($p < 0.0001$; ►Table 4). Those with AKI had a 59% higher count of weeks on respiratory support (including both invasive and noninvasive ventilator support) than those without AKI (count

ratio = 1.59, 95% CI: 1.14–2.23; ►Supplementary Table S3, available in the online version). Compared with those without AKI, infants with AKI more frequently required longer duration of supplemental oxygen ($p < 0.0001$) (►Table 4). Those with AKI had a 43% increased count of weeks of oxygen requirement within the first 4 weeks after birth compared with those without AKI (count ratio = 1.43, 95% CI: 1.22–1.68; ►Supplementary Table S4, available in the online version).

Discussion

The results of our study show that AKI is independently associated with worse lung outcomes in infants born ≥32 weeks of GA. After controlling for potential confounders, infants with AKI were more likely to develop CLD/death and to require longer duration of oxygen and respiratory support.

These findings supplement the current literature by finding an association between AKI and lung disease that extends to infants ≥32 weeks. Others have published similar results in premature infants, and pediatric and adult critically-ill cohorts have shown an association between AKI and lung disease.[14,24,25] Studies assessing mortality and pulmonary outcomes in other critically-ill patient populations with AKI report similar findings.[8,26,27]

In addition to demonstrate an association between AKI and CLD/death, we explored the association of AKI and other pulmonary outcomes (weeks of oxygenation and weeks of respiratory support). We found an independent association between AKI and longer durations of respiratory support and oxygen dependence. Taken together, these findings suggest that AKI is associated with a higher rate of CLD, as well as longer durations of respiratory support and supplemental oxygen therapy in infants' ≥32 weeks of GA at birth. Our findings are similar to findings in cohorts of critically-ill children, where those with AKI had a longer duration of mechanical ventilation and intensive care unit admission, as well as higher oxygenation indices, during their critical illness than those without kidney injury.[8,28]

There are several possible explanations for our findings. First, as the infants in this cohort were admitted to the NICU, they may have had a high rate of multisystem organ dysfunction and were critically ill. It is possible that despite our best attempts to control for potential confounding, critically-ill infants may get both AKI and CLD. Second, experimental research suggests an "endocrine" role of the kidney, following AKI, which results in a cascade of inflammatory responses disrupting lung homeostasis.[10] While the mechanisms require further elucidation, this interaction between kidney and lung has been demonstrated in animal models, with upregulation of apoptosis-regulating genes in mouse lungs after ischemic AKI and cytokine activation resulting in pulmonary injury and fibrosis.[11] Studies in mice after ischemic AKI show a response in the lung similar to the kidney inflammatory response.[26] Third, the relationship between AKI and poor lung outcomes could represent a complex interaction between AKI and mechanical ventilation, as AKI increases pulmonary neutrophil activity and increases the sensitivity of lungs to injury.[11] Similar to what has been described in the acute respiratory distress syndrome literature, AKI may alter inflammation on a systemic basis and lead to an inflammatory response in the lung and other organs.[10,13]

We also observed that infants whose mothers had polyhydramnios were more likely to have CLD/death than those without polyhydramnios (13.4 vs. 3.6%; p <0.001). Polyhydramnios has been associated with decreased fetal lung maturity indices in infants.[29] While the mechanism for these changes remains unclear, infants with polyhydramnios had less mature lung parenchyma at delivery based on lecithin/sphingomyelin ratios, phosphatidylglycerol, and lamellar bodies counts.[29] Polyhydramnios could also be a sign of impaired swallowing and/or neurologic impairment. This finding deserves additional investigation.

To our knowledge, this is the first study to examine the associations between AKI and lung disease in infants born later preterm and term. We used a contemporary definition of AKI including both serum creatinine and urinary output criteria and a standard definition of CLD. Despite the strengths of this study, we acknowledge several important limitations. While utilizing AKI based on KDIGO definitions for infants is the current standard for this patient population, given the normal trajectory of decreasing creatinine over the first several days of age, this may not be the optimal threshold for evaluation of kidney dysfunction in this patient population. We acknowledge the limitations of serum creatinine and the lack of rigorous testing of this definition in infants. However, the most recent workshop by National Institute of Health (NIH) on neonatal AKI provided expert guidance that this is the best assessment of neonatal AKI at this time.[17] Additionally, we included urine output criteria where available, which in- creased the diagnosis rate of AKI among a neonatal population, but acknowledge that there is little evidence in infants for the empiric thresholds. Given that the definition of CLD is evolving and that 28 days may be too early to assign the diagnosis, we explored a secondary outcome of a weekly measure of ventilatory and oxygen support, a new metric that has not been previously explored or validated.[30] We also note that there are primary pulmonary factors (e.g., pneumonia) which may also contribute to the development of lung diseases which are not evaluated due to our study design. Finally, as enrolled infants were from many neonatal ICUs with various standards of clinical care, differences in respiratory management may have contributed to the differences seen in CLD rates and other respiratory outcomes as the current definition of CLD used both clinically and for this study is an imprecise method to determine long-term pulmonary outcome.[31]

Conclusion

In conclusion, we show that in infants born ≥32 weeks of GA, AKI is independently associated with CLD/mortality and that infants with AKI required longer durations of respiratory support. Given the long-term implications of CLD, as well as extended durations of ventilator and oxygen dependence on childhood lung function, our findings suggest further study to evaluate if AKI plays a modifiable role in pulmonary outcomes in this patient population. Further work is needed to under- stand the interaction between lung and kidney and the potential role of inflammatory markers and cytokine response to both lung and kidney injury in this patient population. Better understanding of these mechanisms may lead to targeted interventions designed to prevent and mitigate AKI and its consequences which may improve the morbidity and mortality of lung and kidney disease in infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163(07):1723–1729 [PubMed: 11401896]
2. Raju TN. Late-preterm births: challenges and opportunities. Pediatrics 2008;121(02):402–403 [PubMed: 18245431]
3. Martin JA, Kirmeyer S, Osterman M, Shepherd RA. Born a bit too early: recent trends in late preterm births. NCHS Data Brief 2009; (24):1–8
4. Engle WA, Tomashek KM, Wallman C; Committee on Fetus and Newborn, American Academy of Pediatrics. "Late-preterm" infants: a population at risk. Pediatrics 2007;120(06):1390–1401 [PubMed: 18055691]
5. Escobar GJ, Clark RH, Greene JD. Short-term outcomes of infants born at 35 and 36 weeks gestation: we need to ask more questions. Semin Perinatol 2006;30(01):28–33 [PubMed: 16549211]
6. Johnson TJ, Patel AL, Jegier BJ, Engstrom JL, Meier PP. Cost of morbidities in very low birth weight infants. J Pediatr 2013;162 (02):243–49.e1
7. Russell RB, Green NS, Steiner CA, et al. Cost of hospitalization for preterm and low birth weight infants in the United States. Pediatrics 2007;120(01):e1–e9 [PubMed: 17606536]
8. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL; AWARE Investigators. Epidemiology of acute kidney injury in critically ill children and young adults. N Engl J Med 2017;376(01):11–20 [PubMed: 27959707]
9. Jetton JG, Boohaker LJ, Sethi SK, et al.; Neonatal Kidney Collaborative (NKC). Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. Lancet Child Adolesc Health 2017;1(03):184–194 [PubMed: 29732396]
10. Basu RK, Wheeler DS. Kidney-lung cross-talk and acute kidney injury. Pediatr Nephrol 2013;28(12):2239–2248 [PubMed: 23334385]
11. 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(01):L3–L11 [PubMed: 18849441]

12. Levy EM, Viscoli CM, Horwitz RI. The affect of acute renal failure on mortality. A cohort analysis. JAMA 1996;275(19):1489–1494 [PubMed: 8622223]
13. Li X, Hassoun HT, Santora R, Rabb H. Organ crosstalk: the role of the kidney. Curr Opin Crit Care 2009;15(06):481–487 [PubMed: 19851101]
14. Askenazi D, Patil NR, Ambalavanan N, et al. Acute kidney injury is associated with bronchopulmonary dysplasia/mortality in pre- mature infants. Pediatr Nephrol 2015;30(09):1511–1518 [PubMed: 25808019]
15. Jetton JG, Guillet R, Askenazi DJ, et al.; Neonatal Kidney Collaborative. Assessment of worldwide acute kidney injury epidemiology in neonates: design of a retrospective cohort study. Front Pediatr 2016;4(10):68 [PubMed: 27486571]
16. Jetton JG, Askenazi DJ. Update on acute kidney injury in the neonate. Curr Opin Pediatr 2012;24(02):191–196 [PubMed: 22227783]
17. Zappitell M, Ambalavanan N, Askenaz DJ, et al. Developing a neonatal acute kidney injury research definition: a report from the NIDDK neonatal AKI workshop. Pediatr Res 2017;82(04):569–573 [PubMed: 28604760]
18. Selewski DT, Charlton JR, Jetton JG, et al. Neonatal acute kidney injury. Pediatrics 2015;136(02):e463–e473 [PubMed: 26169430]
19. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care 2013;17(01):204 [PubMed: 23394211]
20. Sutherland SM, Byrnes JJ, Kothari M, et al. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. Clin J Am Soc Nephrol 2015;10(04):554–561 [PubMed: 25649155]
21. Schneider J, Khemani R, Grushkin C, Bart R. Serum creatinine as stratified in the RIFLE score for acute kidney injury is associated with mortality and length of stay for children in the pediatric intensive care unit. Crit Care Med 2010;38(03): 933–939 [PubMed: 20124891]
22. Balena-Borneman J, Ambalavanan N, Tiwari HK, Griffin RL, Hal-loran B, Askenazi D. Biomarkers associated with bronchopulmonary dysplasia/mortality in premature infants. Pediatr Res 2017; 81(03):519–525 [PubMed: 27893721]
23. Noh M, Lee Y. Extended negative binomial hurdle models. Stat Methods Med Res 2018;1:962280218766567
24. Oh W, Poindexter BB, Perritt R, et al.; Neonatal Research Network. 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(06): 786–790 [PubMed: 16356432]
25. 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 (São Paulo) 2010;65 (07):663–674 [PubMed: 20668623]
26. 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(03):547–558 [PubMed: 18235097]
27. Madershahian N, Liakopoulos OJ, Wippermann J, et al. The impact of intraaortic balloon counterpulsation on bypass graft flow in patients with peripheral ECMO. J Card Surg 2009;24(03):265–268 [PubMed: 19438779]
28. 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(03):253–258 [PubMed: 21760565]
29. Piazze JJ, Maranghi L, Cosmi EV, Anceschi MM. The effect of polyhydramnios and oligohydramnios on fetal lung maturity indexes. Am J Perinatol 1998;15(04):249–252 [PubMed: 9565223]
30. Jensen EA, Wright CJ. Bronchopulmonary Dysplasia: The Ongoing Search for One Definition to Rule Them All. J Pediatr 2018; 197:8–10 [PubMed: 29605396]
31. Allen J, Zwerdling R, Ehrenkranz R, et al.; American Thoracic Society. Statement on the care of the child with chronic lung disease of infancy and childhood. Am J Respir Crit Care Med 2003; 168(03):356–396 [PubMed: 12888611]

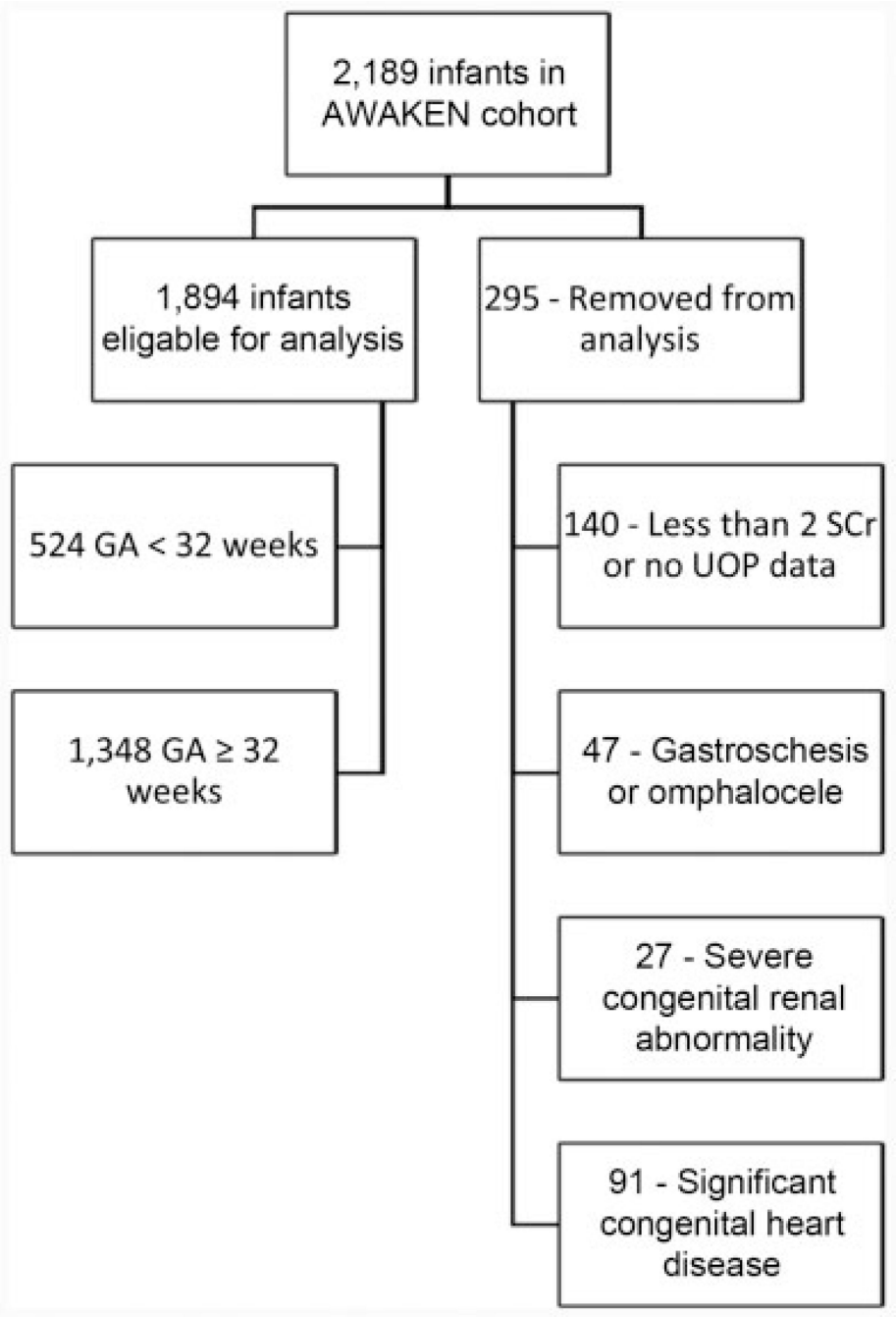

Fig. 1.

Breakdown of the eligible, enrolled and nonenrolled infants in the study cohort. AWAKEN, assessment of worldwide acute kidney injury epidemiology in neonates; GA, gestational age; SCr, serum creatinine; UOP, urine output.

Table 1

Univariate characteristics for infants with and without chronic lung disease (CLD) or death at 28 days of life

Infant characteristics	No CLD *n* = 1,244 (%)	CLD/Death *n* = 104 (%)	*p*-Value[a]
Sex (male)	699 (56.2)	56 (53.8)	0.78
Ethnicity			
Hispanic	157 (12.6)	11 (10.6)	0.61
Non-Hispanic	878 (70.6)	72 (69.2)	
Unknown	209 (16.8)	21 (20.2)	
Race			
White	717 (57.6)	60 (57.7)	0.79
Black	200 (16.1)	19 (18.3)	
Other	327 (29.3)	25 (24.0)	
Mean gestational age (wk)	36.1 ± 2.7	36.1 ± 2.6	0.80
Mean birth weight (g)	2,662 ± 812	2,627 ± 902	0.67
Median 1-min Apgar's score	8 (5–8)	5 (3–8)	<0.0001
Median 5-min Apgar's score	9 (8–9)	8 (6–9)	<0.0001
Maternal characteristics			
Multiple gestations	184 (14.8)	8 (7.7)	0.05
Intrapartum infection	104 (8.4)	6 (5.8)	0.35
Diabetes	183 (14.7)	14 (13.5)	0.73
Hypertension	105 (8.4)	7 (6.7)	0.54
Hydramnios			
Oligohydramnios	65 (5.2)	3 (2.9)	0.0005
Normohydramnios	1133 (91.1)	89 (85.6)	
Polyhydramnios	46 (3.7)	12 (11.5)	
Steroids for fetal maturation	313 (25.2)	18 (17.3)	0.07
Infant characteristics			
Neonatal intubation	174 (14.0)	49 (47.1)	<0.0001
Meconium at delivery	165 (13.3)	19 (18.3)	0.15

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Infant characteristics	No CLD *n* = 1,244 (%)	CLD/Death *n* = 104 (%)	*p*-Value[a]
Hypoxic-ischemic encephalopathy	89 (7.2)	13 (12.5)	0.05

Note: Data in table are presented as the *n* (%), mean standard deviation, or median (interquartile range).

[a] *p*-Value for all variables was estimated using chi-square for categorical, *t*-test for comparing means, and Wilcoxon's rank sums for comparing Apgar's scores.

Table 2

Association between AKI and CLD or death at 28 days of life

	No CLD *n* = 1,244 (%)	**Mild/moderate CLD *n* = 56 (%)**	**Severe CLD/death *n* = 48 (%)**
AKI[a]			
No AKI	945 (76.0)	23 (41.1)	18 (37.5)
AKI	299 (24.0)	33 (58.9)	30 (62.5)
Odds ratio (95% CI)	Referent	4.54 (2.62–7.84)	5.27 (2.90–9.59)
AKI stages[b]			
Stage-1 AKI	149 (12.0)	11 (19.6)	11 (22.9)
Stage 2/3 AKI	150 (12.1)	22 (39.3)	19 (39.6)
Odds ratio (95% CI)	Referent	4.63 (2.79–7.68)	5.02 (2.91–8.65)
AKI type[c]			
UOP only	185 (61.9)	7 (21.2)	9 (30.0)
SCr only	88 (29.4)	19 (57.6)	15 (50.0)
Odds ratio (95% CI)	Referent	5.71 (2.31–14.08)	3.50 (1.48–8.32)
SCr and UOP	26 (8.7)	7 (21.2)	6 (20.0)
Odds ratio (95% CI)	Referent	7.12 (2.31–21.92)	4.74 (1.56–14.42)

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CLD, chronic lung disease; SCr, serum creatinine; UOP, urine output. Note: Data in table are presented as the number with the percentage in parenthesis.

[a]Odds ratios estimated from unconditional logistic regression.

[b]Odds ratios estimated from ordinal logistic regression.

[c]Odds ratios estimated among those with AKI from multinomial logistic regression with urine output as the referent group.

Table 3

Crude and adjusted odds ratios (ORs)[a] and associated 95% confidence intervals (CIs) for chronic lung disease or death at 28 days of life

Characteristics	Crude OR (95% CI)	Adjusted[b] OR (95% CI)	*p*-Value[b]
Acute kidney injury	4.89 (3.21–7.35)	4.57 (2.92–7.17)	<0.0001
Gestational age (wk)	1.01 (0.94–1.07)	0.88 (0.81–0.96)	0.005
Maternal polyhydramnios	3.40 (1.74–6.64)	1.67 (0.78–3.55)	0.18
Multiple gestations	0.48 (0.23–1.00)	0.47 (0.21–1.05)	0.07
Neonatal Intubation	5.48 (3.61–8.31)	4.88 (3.12–7.61)	<0.0001

[a]Estimated from logistic regression.

[b]Adjusted for other variables in the model.

Table 4

Comparison of unadjusted weeks of mechanical ventilator support in first 4 weeks among infants with and without acute kidney injury

	No AKI (*n* = 986)	AKI (*n* = 362)	*p*-Value[a]
Any oxygen support (%)			
0 wk	89.4	72.4	<0.0001
1 wk	3.5	7.5	
2 wk	5.6	9.4	
3 wk	0.6	4.1	
4 wk	0.9	6.6	
Invasive mechanical ventilation weeks (%)			
0 wk	94.5	78.5	<0.0001
1 wk	1.5	5.0	
2 wk	2.9	8.6	
3 wk	0.5	4.1	
4 wk	0.5	3.9	
CPAP/noninvasive ventilation (%)			
0 wk	93.9	89.8	0.0249
1 wk	3.3	6.4	
2 wk	2.5	3.3	
3 wk	0.0	0.0	
4 wk	0.2	0.6	
High FiO_2 weeks[b] (%)			
0 wk	88.4	75.7	<0.0001
1 wk	4.6	9.7	
2 wk	5.2	8.8	
3 wk	0.9	3.9	
4 wk	0.9	1.9	
Low FiO_2 weeks[c] (%)			
0 wk	81.6	71.0	<0.0001
1 wk	8.2	12.2	
2 wk	8.4	12.2	
3 wk	1.3	3.3	
4 wk	0.4	1.4	

Abbreviation: FiO_2, fraction of inspired oxygen.

[a]Estimated from a Cochran–Mantel–Haenszel test statistic.

[b]Fraction of inspired oxygen (FiO_2) ≥0.30.

[c]Fraction of inspired oxygen (FiO_2) <0.30.