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Is Neonatal Acute Kidney Injury an Independent Risk Factor for Poor Neurodevelopmental Outcomes in Extremely Low Gestational Age Neonates (ELGAN)s 22 0/7 – 27 6/7?

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Abstract

Objective: To compare 2-year neurodevelopmental outcomes in extremely low gestational age neonates (ELGANs) with and without acute kidney injury (AKI).

Study Design: A retrospective cohort study of 531 infants born at ≤27 6/7 weeks gestational age (2009–2019). Outcomes included cerebral palsy, Bayley-III scores, and a composite of neurodevelopmental impairment (NDI <85) or death.

Result: In univariable analysis, neonatal AKI was significantly associated with the composite outcome of NDI <85 or death. However, this association was attenuated and no longer statistically significant after adjusting for clinical characteristics.

Conclusion: In adjusted analyses, AKI was not significantly associated with neurodevelopmental impairment or death.

Introduction

Measures of neurodevelopmental outcomes in preterm infants are essential for not just evaluating our therapies and neonatal care but also in identifying long term needs that an infant might have.[1] Early recognition of neurodevelopmental impairment can aid in counseling and prognosis and timely referral of the patient to the appropriate intervention programs in order to facilitate enhancement of their greatest potential.[2] Several morbidities of extreme prematurity have shown to be independently associated with poor neurodevelopmental outcomes. These are intraventricular hemorrhage,[3-4] bronchopulmonary dysplasia,[5] patent ductus arteriosus[6] and necrotizing enterocolitis.[7]

Neonatal kidney development begins during third week of gestation and continues until full term.[8-10] In mouse models, premature differentiation of nephrons can deplete progenitors and lead to hypoplastic kidneys.[11] In addition, the normal window of nephrogenesis closes near 36 weeks gestation, with almost two-thirds of human nephrons forming during the 3rd trimester.[12-14] This highlights the impact of preterm birth on nephron development.

The definition of acute kidney injury in neonates has evolved over the past decade. In addition, there is evidence to show that serum creatinine concentration in extremely low birth weight (ELBW) infants differ at varying gestational age.[15] The overall incidence of AKI reported in the Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN) study was 29.9%, and those with AKI had greater than 4-fold increased odds of death and longer hospital length of stay. Even after adjusting for multiple potential confounding factors, infants with AKI had higher mortality compared to those without AKI (9.7% vs 1.4%). Interestingly, in a patient cohort of 22-29 weeks gestational age (WGA) neonates, they found that the incidence of AKI was at 48%.[15] Nevertheless, there are very few studies that look at the association between AKI and neurodevelopmental impairment in literature.[16] [17] The purpose of this retrospective chart review study is to determine whether neonatal AKI is independently associated with poor

neurodevelopmental outcomes or death in extremely low birth weight neonates (ELGANs) born at 22 0/7 - 27 6/7 WGA.

Methods

This was an Institutional Review Board (IRB) approved research by the University Hospital Cleveland Medical Center IRB with waiver of consent. We conducted a single center retrospective chart review of infants ≤ 27 6/7 WGA born at Rainbow Babies and Children's Hospital (Cleveland, OH) a Level IV, 82-bed Neonatal Intensive Care Unit (NICU). Inclusion criteria were birth between January 1, 2010, and December 31, 2019, at 22 0/7–27 6/7 WGA and documented serum creatinine throughout hospitalization. Infants who died within 7 days of admission, were excluded. Infants who died after 7 days of admission were included in the composite outcome of NDI <85 or death. Exclusion criteria included patients with lethal chromosomal anomalies, severe congenital anomalies including those of the kidneys and urinary tracts (CAKUT) such as bilateral renal hypoplasia, bilateral cystic kidney disease, posterior urethral valves, prune belly (Eagle Barrett) syndrome, bilateral moderate-to-severe hydronephrosis, bilateral vesicoureteral reflux, autosomal recessive polycystic kidney disease (ARPKD), congenital nephrotic syndrome, and congenital heart disease requiring surgical repair within 7 days of life.

Maternal and Neonatal: Demographics and Characteristics

Maternal Characteristics: Maternal hypertension (mHTN) refers to any recorded diagnosis of hypertension during pregnancy, whether it is acute or chronic. Maternal diabetes refers to any recorded diagnosis of gestational diabetes or diabetes mellitus before pregnancy. Chorioamnionitis was defined by either histopathological chorioamnionitis, documented on the placental pathology report, or clinical chorioamnionitis as defined by two or more of maternal fever, uterine tenderness, malodorous amniotic fluid, maternal of fetal tachycardia or evidence of inflammation.

Neonatal Characteristics: AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) modified for neonates adapted from the AWAKEN study[15] where each serum creatinine (SCr) peak was compared with the lowest prior SCr during a period of +/- 7 days to detect both an absolute and percent rise from baseline. An increase in serum creatinine by 0.3mg/dL or more within 48 hours, or an increase in serum creatinine to 1.5 times baseline or more within the last 7 days meet criteria for AKI. Infants were grouped according to stage of acute kidney injury based on modified KDIGO criteria. Additional neonatal characteristics include Score for Neonatal Acute Physiology (SNAP) which correlates to severity of illness. [17] Because birth weight and SNAP score were highly correlated, only one of these variables was included in the multivariable model. SNAP score was selected as a measure of illness severity, as inclusion of both variables resulted in collinearity. Bronchopulmonary dysplasia (BPD) was defined using the Jensen criteria which requires respiratory support at 36 weeks post menstrual age.[18] Patent ductus arteriosus (PDA) was diagnosed based on clinical or echocardiographic examination. Grade III Intraventricular hemorrhage (IVH) was characterized by intraventricular hemorrhage with acute ventricular dilation, grade IV IVH characterized by extension of the hemorrhage into the surrounding brain parenchyma and periventricular leukomalacia (PVL) was defined as the presence of cystic lesions in the periventricular area observed on any cranial ultrasound during the neonatal stay. Early and late sepsis were defined as a positive blood culture at any time during the neonatal admission. Necrotizing enterocolitis (NEC) was defined according to Bell's Staging Criteria of stage IIA or higher. Small for gestational age (SGA) was defined by birth weight less than 10th percentile for gestational age per Fenton Calculator.[19]

Neurodevelopmental Outcomes

The Bayley Scales of Infant and Toddler Development [20] (Bayley-III Third Edition) was administered to children between 18-24 months of corrected age by a psychologist who had been certified in Bayley test administration. The Bayley-III is used to assess a child's developmental functioning and identify developmental delays in three general areas: cognition,

language and motor functioning. Standardized scores were calculated using the child's corrected age. Missing Bayley and Cognitive motor scores were adjudicated. Patients were also assessed for blindness, deafness and cerebral palsy during this assessment. Neurodevelopmental impairment (NDI) was defined as the presence of any of the following: moderate-to-severe cerebral palsy (CP), severe visual impairment, deafness, or a cognitive, motor, or language score <85 (−1 SD). NDI <85 or death was defined as NDI based on a Bayley-III cognitive, motor, or language score <85, blindness, deafness, or CP, or death. CP was defined as a non-progressive condition affecting the central nervous system, characterized by abnormal muscle tone or reflexes in at least one limb with impaired movement or postural control that interferes with age-appropriate activities. CP severity was classified using the Gross Motor Function Classification System (GMFCS), with a GMFCS level ≥2 used to define moderate-to-severe CP for the purposes of this study. Thus, children with isolated mild motor findings, such as tight heel cords, who did not meet the GMFCS threshold were not classified as having CP. Deafness was defined as permanent bilateral hearing loss requiring amplification, and blindness was defined as permanent bilateral loss of vision.

Sample Size Estimate

With a total sample size of 300 participants, equally distributed by AKI status, the study has approximately 90% to 100% power to detect odds ratios ranging from 2.0 to 5.0 at a two-sided significance level of 0.05.

Statistical Analysis

Variables associated with the study outcomes, including demographic, clinical, and socioeconomic factors were presented as frequency and percentages for categorical variables; median and interquartile ranges for continuous variables. Generalized Estimating Equation (GEE) univariable models were fit to examine the individual associations between each predictor/variable with the study outcome. Significant predictors (p-Value < 0.05) from the univariable analyses were included in a multivariable GEE model to adjust for potential

confounding effects. The analysis accounted for clustering by multiple births. Exchangeable correlation structure was used as this assumes a homogenous correlation and accounts for the Intra-Cluster Correlation (ICC). Results from both the univariable and multivariable analyses were presented as odds ratios with 95% Confidence intervals and p-values. All the analyses were performed in R software, version 4.1.3 and IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA)

Data Collection

Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at University Hospitals.[21, 22]

Results

A total of 531 infants were born at 22 0/7–27 6/7 WGA during the study period. Of these, 61 died within 7 days of admission, 97 of the survivors did not complete neurodevelopmental follow-up at 18-22 months and so were not included, and 4 met predefined exclusion criteria (3 with lethal chromosomal anomalies and 1 with severe CAKUT). Therefore, 369 infants met the study inclusion criteria. Among these infants, 39 died after 7 days of admission and 330 completed neurodevelopmental follow-up at 18–22 months corrected age. Missing Bayley cognitive and motor scores were adjudicated (2 missing cognitive scores and 13 missing motor scores were adjudicated according to general pediatrics outcomes). Missing language scores were not adjudicated because most of these patients were deemed uncooperative or had a tracheostomy in place during their follow-up assessment (Fig. 1).

Patient Characteristics

Maternal and neonatal demographics are shown in table 1. The median birthweight was 710g. The median SNAP score was 49. Most of the patient sample had public insurance (77.8%) and 52.1% of the mothers had education level of high school or less. Infants who experienced NDI <85 or death had lower birth weight and gestational age and higher SNAP scores compared

with infants without NDI <85 or death. Maternal age, sex, multiple gestation, race, maternal education, maternal hypertension, maternal diabetes, and low APGAR scores did not differ significantly between groups. Among neonatal morbidities, PDA, AKI, and BPD were more common among infants who experienced NDI <85 or death, whereas the frequencies of NEC/SIP, severe IVH/PVL, and sepsis did not differ significantly between groups.

Neurodevelopmental Outcome Among Infants with AKI

Table 2 details the univariable associations between AKI and individual or composite neurodevelopmental outcomes. Overall, the incidence of the primary composite outcome of NDI <85 or death was 86.7%, and this incidence was significantly higher among infants with AKI compared to those without (90.7% vs. 81.8%; OR 2.17, 95% CI 1.19–3.98, p=0.012). Infants with AKI also had significantly higher rates of severe overall impairment (NDI <70 or death: 56.9% vs. 44.8%, p=0.015) and more than double the odds of cerebral palsy or death (31.0% vs. 14.5%; OR 2.55, 95% CI 1.54–4.22, p<0.001). When evaluating specific Bayley-III domains, AKI was significantly associated with worse outcomes in both cognitive and motor functions at both the <85 and <70 thresholds. Most notably, motor scores <70 or death occurred in 38.2% of the AKI group versus 21.8% of the no-AKI group (p<0.001). Similarly, while language impairment (score <85) or death affected 77.1% of all assessed patients, infants with AKI trended toward a higher burden of this outcome (81.1% vs. 72.1%, p=0.053). Notably, 42 infants were missing language scores, primarily due to an inability to cooperate during the exam.

Unadjusted and Adjusted Neurodevelopmental Outcomes

Table 3 provides a comparative analysis of neonatal characteristics between two groups of infants: those with neurodevelopmental impairment (NDI) (defined by any Bayley-III score <85 or CP, deafness, blindness) or who had died, versus those who survived at 2 years corrected age with Bayley-III scores all 85 or higher. The table includes both univariable and multivariable analyses, detailing their respective odds ratios (OR), confidence intervals (CI), and p-values. In univariable analysis, AKI was significantly associated with increased odds of the composite

outcome of NDI <85 or death (OR 2.17, 95% CI 1.19–3.98; p=0.012), as were SNAP, PDA, and public insurance. Conversely, chorioamnionitis was univariately associated with decreased odds of the composite outcome (OR 0.48, 95% CI 0.27–0.88; p=0.017). In the multivariable model adjusting for these clinical covariates, AKI was no longer significantly associated with NDI <85 or death (adjusted OR 1.28, 95% CI 0.62–2.67; p=0.502), and SNAP similarly lost statistical significance (adjusted OR 1.01, 95% CI 0.99–1.03; p=0.201). Factors that remained independently associated with increased odds of the composite outcome included the presence of a PDA (adjusted OR 1.97, 95% CI 1.02–3.80; p=0.043) and public insurance (adjusted OR 2.35, 95% CI 1.18–4.69; p=0.016). Additionally, the inverse association between chorioamnionitis and adverse outcomes remained borderline significant in the multivariable analysis (adjusted OR 0.53, 95% CI 0.28–1.00; p=0.050). BPD was not included in the multivariable analysis because it is defined at 36 weeks postmenstrual age and may occur downstream of AKI and other neonatal morbidity, potentially representing part of the pathway between AKI and the composite outcome of NDI <85 or death.

Discussion

This 10-year retrospective analysis of a single-center cohort of ELGANs born at 22 0/7–27 6/7 WGA found that although AKI is univariately associated with NDI <85 or death, it is not associated after adjusting for covariates. The attenuation of the association after adjustment suggests that the observed relationship between AKI and adverse neurodevelopmental outcome may overlap substantially with the broader severity and complexity of illness and degree of immaturity experienced by extremely premature infants. The lack of a significant adjusted association between AKI and the composite outcome was consistent across the individual neurodevelopmental outcomes evaluated in this study. In multivariable analyses, AKI was not significantly associated with death or individual measures of neurodevelopmental impairment, including Bayley-III cognitive, language, or motor scores <70 or <85, deafness,

blindness, or cerebral palsy. Conversely, our multivariable model did identify other factors independently associated with the composite outcome, including public insurance and the presence of a PDA. Interestingly, clinical chorioamnionitis demonstrated an inverse association with NDI <85 or death.

Our findings add to a body of heterogeneous literature studying the association between neonatal AKI and subsequent neurodevelopmental outcomes in preterm infants. Few prior studies have assessed the association of AKI and neurodevelopmental impairment in extremely premature neonates. In a secondary analysis of the Preterm Erythropoietin Neuroprotection Trial (PENUT), Hanna et al. evaluated 24–27 WGA infants and found that AKI was associated with the composite outcome of death or moderate-to-severe neurodevelopmental impairment after adjustment (adjusted OR 1.53, 95% CI 1.07–2.18), as well as cognitive Bayley-III scores <85 (adjusted OR 1.94, 95% CI 1.25–2.99).[23] In contrast, King et al. studied 203 very low birth weight infants and found that although AKI was associated with neurodevelopmental impairment in bivariate analysis (RR 1.67, 95% CI 1.18–2.36), the association was no longer significant after adjustment (adjusted RR 1.07, 95% CI 0.68–1.68).[24] Similarly, Beghetti et al. evaluated 339 very preterm or very low birth weight infants and found an association between AKI and worse neurodevelopmental outcomes in unadjusted analyses that was no longer significant after adjustment for neonatal comorbidities.[25] Yen et al. also reported an association between sustained AKI and neurodevelopmental and growth outcomes in a single NICU center.[26] Earlier work by Bruel et al. evaluated critical serum creatinine values in very preterm newborns and also found an association with adverse outcomes, although the population and definition of kidney injury differed from those used in our study.[27] Differences in gestational age, AKI definitions, timing of AKI assessment, outcome definitions, and covariate adjustment may contribute to the heterogeneous findings across studies.

Only a few of these studies (Yen et al., Hanna et al., Beghetti et al.) utilized the AKI definition adapted from the AWAKEN study,[15] which was the same definition used in this analysis. The

timing of AKI assessment may also contribute to differences between studies. In our study, AKI was evaluated throughout the neonatal hospitalization, whereas some prior studies focused on AKI during an earlier period of hospitalization. AKI and other neonatal morbidities may also be highly correlated because they can reflect the severity and complexity of illness in extremely premature infants. This overlap may make it difficult to distinguish the independent contribution of AKI to neurodevelopmental outcomes and may complicate interpretation of the adjusted regression estimates.

Lingasubramanian et al. showed that in their patient cohort with NEC, 70% had AKI and onset of AKI mostly precedes NEC onset, with moderate to severe AKI being more prevalent than the milder form in infants with NEC.[28] Adcock et al. illustrated that infants with AKI had 2.4-fold increase risk of IVH (OR 2.38, 95% CI 1.46–3.87) and a 3.5-fold increased risk of severe IVH (OR 3.45, 95% CI 1.98–6.04).[29] These findings highlight the interconnected nature of AKI and other complications of extreme prematurity. The attenuation of the association after adjustment suggests that the observed relationship between AKI and adverse neurodevelopmental outcomes may be partly explained by clinical factors related to illness severity, complexity of neonatal course and degree of prematurity.

The inverse association we observed between chorioamnionitis and the composite outcome of NDI <85 or death adds another layer of complexity to these clinical factors. While chorioamnionitis is a known driver of preterm delivery,[30] its independent impact on long-term neurodevelopment remains highly debated. Some literature suggests an association with increased risk of cerebral palsy,[31,32] while other studies have described a "preconditioning" effect where antenatal inflammation accelerates fetal lung and tissue maturation, potentially offering a survival advantage. [33,34,35]Additionally, this finding may be influenced by survival bias in the most extremely premature infants.[36]

BPD was not included in the multivariable analysis because it is defined at 36 weeks postmenstrual age and was therefore unavailable for the 27 infants who died before reaching

this time point. Including BPD in the model would have excluded these infants from the analysis despite death being a component of the composite outcome. In addition, because BPD is a later-occurring neonatal morbidity, it may occur downstream of AKI and other neonatal complications and should be considered part of the clinical course rather than a baseline characteristic.

To our knowledge, few studies have specifically examined the association between neonatal AKI and neurodevelopmental outcomes in ELGANs, particularly those born at 22–27 WGA. Our study adds to this literature by evaluating AKI throughout the neonatal hospitalization in a cohort of ELGANs and examining a broad range of neurodevelopmental outcomes. Follow-up during the final 2 years of the study was affected by the COVID-19 pandemic. Additional strengths include structured neurodevelopmental assessments and evaluation of multiple domains of neurodevelopmental outcome.

This study has several limitations. First, AKI was defined using serum creatinine levels alone, without incorporating urine output because of the difficulty in accurately assessing urine output from electronic medical records. As a result, some episodes of AKI, particularly those identified by urine output criteria, may have been missed. In addition, serum creatinine can be difficult to interpret in premature neonates because creatinine levels may be influenced by muscle mass. Second, some Bayley-III language scores were unavailable, and NDI classification in these cases was based on the available cognitive and motor domains and other components of the NDI definition. The absence of language scores may have resulted in under classification of NDI in some infants and reduced the statistical power to detect meaningful associations. Finally, some neurodevelopmental follow-up were incomplete, resulting in variable denominators across individual neurodevelopmental outcomes. Infants who died before the 18–22-month assessment could not undergo Bayley-III testing but were included in the composite outcomes of NDI or death. Thus, the composite outcomes incorporated mortality, whereas analyses of individual neurodevelopmental measures were limited to infants with available follow-up. These

differences in outcome ascertainment should be considered when interpreting the individual neurodevelopmental outcomes.

Conclusion

In this extensive retrospective analysis of a single-center cohort of ELGANs born between 22 0/7 and 27 6/7 WGA, acute kidney injury was initially found to be univariately associated with neurodevelopmental impairment or mortality. However, this association was no longer observed after adjustment for relevant clinical covariates. This pattern was consistent across individual measures of neurodevelopmental outcome, including death, Bayley-III domain scores, deafness, blindness, and cerebral palsy. This attenuation of the association after adjustment suggests that the relationship between AKI and adverse neurodevelopmental outcomes may be largely mediated by underlying illness severity and degree of immaturity. These findings highlight the importance of considering AKI within the broader clinical context of the extremely premature infant rather than as an isolated predictor of long-term neurodevelopmental outcome. Further prospective, multicenter studies with standardized assessment of AKI are needed to better define the independent contribution of neonatal AKI to neurodevelopmental outcomes in this vulnerable population.

Ethics approval and consent to participate

This study was approved by the University Hospital Cleveland Medical Center IRB with a waiver of consent.

Data availability

Datasets generated during the study are available from the corresponding author on reasonable request.

Author contributions

D.B. and M.B. conceptualized the study. D.B. performed data collection and curation from electronic medical records and paper charts, and drafted the initial manuscript. D.W.C. conducted the neurodevelopmental follow-up clinics and acquired the clinical outcome data and adjudicated the Bayley-III assessments. S.M. and N.M. performed the formal statistical analyses, with A.M.H. providing statistical support and interpretation. E.J. provided pediatric nephrology expertise and clinical interpretation of the renal data. All authors critically reviewed the manuscript for important intellectual content and approved the final manuscript as submitted.

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Competing interests

The authors declare no competing interests.

Figure 1 – STROBE Diagram of Participants

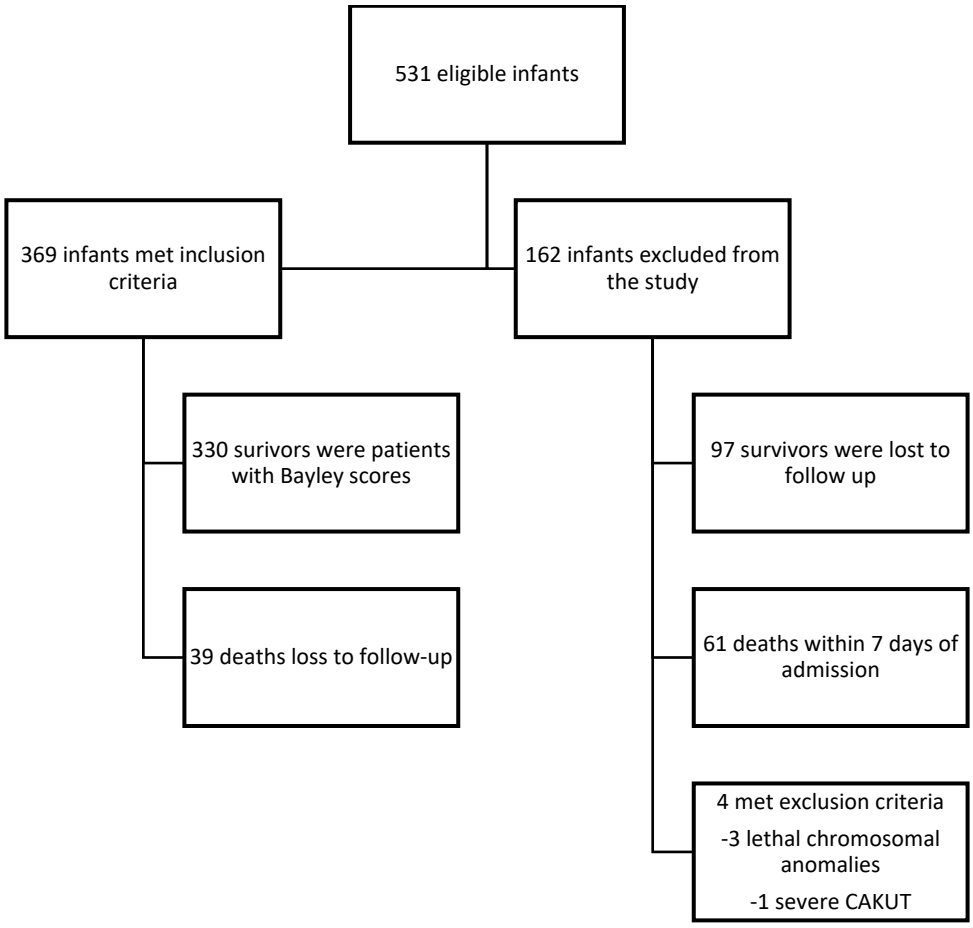

Table 1

Characteristic	NDI <85 or Death	
	No, N = 49[1]	**Yes, N = 320[1]**
Birth weight in kilograms	0.81 (0.71, 0.96)	0.71 (0.60, 0.83)
Sex-Male	24 (49.0%)	183 (57.2%)
Small for Gestational Age	2 (4.1%)	35 (10.9%)
APGAR Score <6	23 (46.9%)	161 (50.3%)
Patent Ductus Arteriosus	19 (38.8%)	206 (64.4%)
Necrotizing Enterocolitis/Spontaneous Intestinal Perforation	2 (4.1%)	26 (8.1%)
Intraventricular Hemorrhage Grade 3 or 4/Periventricular Leukomalacia	4 (8.2%)	57 (17.8%)
Sepsis	11 (22.4%)	59 (18.4%)
Acute Kidney Injury	19 (38.8%)	185 (57.8%)
Bronchopulmonary Dysplasia[1]	28 (57.1%)	224 (76.5%)
Chorioamnionitis	27 (55.1%)	118 (36.9%)
Maternal Age	28 (23, 32)	26 (22, 31)
SNAP Score	42 (24, 55)	49 (33, 65)
Multiple gestation	8 (16.3%)	63 (19.7%)
Race-Black[2]	35 (71.4%)	238 (74.6%)
Maternal Education-High School or Less[3]	20 (41.7%)	152 (53.9%)
Public Insurance	32 (65.3%)	255 (79.7%)
Maternal Hypertension	7 (14.3%)	73 (22.8%)
Maternal Diabetes	1 (2.0%)	20 (6.3%)

1 n (%); Median (IQR)

1. BPD status was unavailable for 27 infants who died before reaching 36 weeks postmenstrual age.
2. Race was missing for one infant who died before neurodevelopmental follow-up.
3. Maternal education data were unavailable for 38 infants who died before neurodevelopmental follow-up, with an additional missing value in the remaining cohort.

Table 2

	AKI	No AKI	p-value	OR (95% CI)
NDI* <70 or death	116/204 (56.9%)	74/165 (44.8%)	0.015	1.68 (1.11, 2.55)
NDI* <85 or death	185/204 (90.7%)	135/165 (81.8%)	0.012	2.17 (1.19, 3.98)
Cerebral Palsy or death**	63/203 (31.0%)	24/165 (14.5%)	<0.001	2.55 (1.54, 4.22)
Bayley Cognitive Score				
<70 or death	69/204 (33.8%)	34/165 (20.6%)	0.004	1.97 (1.25, 3.10)
<85 or death	133/204 (65.2%)	86/165 (52.1%)	0.009	1.76 (1.16, 2.69)
Bayley Motor Score				
<70 or death	78/204 (38.2%)	36/165 (21.8%)	<0.001	2.33 (1.47, 3.68)
<85 or death	150/204 (73.5%)	101/165 (61.2%)	0.006	1.84 (1.19, 2.85)
Bayley Language Score (42 patients missing scores)				
<70 or death	82/180 (45.6%)	63/147 (42.9%)	0.440	1.19 (0.76, 1.86)
<85 or death	146/180 (81.1%)	106/147 (72.1%)	0.053	1.67 (0.99, 2.80)

*NDI was defined by having any one of the following: moderate-severe CP, severe visual impairment, deafness, or cognitive or language score <85 (-1 SD)
**1 patient unknown CP status

Table 3

	NDI <85 or Death		Univariable		Multivariable	
Characteristic	**No**	**Yes**	**OR[1] (95% CI[2])**	**p-value**	**OR[1] (95% CI[2])**	**p-value**
AKI[3]	19 (38.8%)	185 (57.8%)	2.17 (1.19,3.98)	.012	1.28 (0.62,2.67)	.502
SNAP	42 (24,55)	49 (33,65)	1.02 (1.00,1.04)	.014	1.01 (0.99,1.03)	.201
PDA[4]	19 (38.8%)	206 (64.4%)	2.80 (1.53,5.13)	<.001	1.97 (1.02,3.80)	.043
Public Insurance	32 (65.3%)	255 (79.7%)	2.11 (1.10,4.04)	.024	2.35 (1.18,4.69)	.016
Chorioamnionitis	27 (55.1%)	118 (36.9%)	0.48 (0.27,0.88)	.017	0.53 (0.28,1.00)	.050
IVH G3/G4 or PVL[5,6]	4 (8.2%)	57 (17.8%)	2.49 (0.80,7.71)	.115	2.18 (0.69,6.87)	.184
BPD[7]	28 (57.1%)	224 (76.5%)	2.30 (1.24,4.24)	.008	---*	---*

[1]OR = odds ratio
[2]CI = confidence interval
[3]AKI = acute kidney injury
[4]PDA = patent ductus arteriosus
[5]IVH = intraventricular hemorrhage grade 3/grade 4
[6]PVL = periventricular leukomalacia
[7]BPD = bronchopulmonary dysplasia
*** Bronchopulmonary dysplasia (BPD) was excluded from the multivariable model because the diagnosis cannot be established for infants who died prior to 36 weeks' postmenstrual age (n=27)**

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