



CLINICAL RESEARCH ARTICLE

Late onset neonatal acute kidney injury: results from the AWAKEN Study

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BACKGROUND: Most studies of neonatal acute kidney injury (AKI) have focused on the first week following birth. Here, we determined the outcomes and risk factors for late AKI (>7d).

METHODS: The international AWAKEN study examined AKI in neonates admitted to an intensive care unit. Late AKI was defined as occurring >7 days after birth according to the KDIGO criteria. Models were constructed to assess the association between late AKI and death or length of stay. Unadjusted and adjusted odds for late AKI were calculated for each perinatal factor.

RESULTS: Late AKI occurred in 202/2152 (9%) of enrolled neonates. After adjustment, infants with late AKI had higher odds of death (aOR:2.1, $p = 0.02$) and longer length of stay (parameter estimate: 21.9, $p < 0.001$). Risk factors included intubation, oligo- and polyhydramnios, mild-moderate renal anomalies, admission diagnoses of congenital heart disease, necrotizing enterocolitis, surgical need, exposure to diuretics, vasopressors, and NSAIDs, discharge diagnoses of patent ductus arteriosus, necrotizing enterocolitis, sepsis, and urinary tract infection.

CONCLUSIONS: Late AKI is common, independently associated with poor short-term outcomes and associated with unique risk factors. These should guide the development of protocols to screen for AKI and research to improve prevention strategies to mitigate the consequences of late AKI.

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INTRODUCTION

The impact of neonatal acute kidney injury (AKI) is becoming more evident. The AWAKEN study (Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates) has confirmed that AKI is common during NICU admission, occurring in 30% of neonates requiring intravenous fluids for >48 h in the neonatal intensive care unit (NICU). In this cohort, those with at least one episode of AKI at any point in the hospitalization have an increased adjusted length of stay of 9 days and 4.6 times higher independent odds of mortality.^{1,2}

Sick neonates admitted to the NICU have unique risk factors for AKI which may be attributable to immature renal physiology, maternal environment, perinatal events, and iatrogenic insults. The preterm kidney has a short window for postnatal glomerulogenesis and both the preterm and term kidney have an inherently low glomerular filtration rate, predisposing them to AKI. Our group and others have focused on identifying risk factors associated with AKI within the first week after birth.³ However, few studies have assessed the impact of AKI later in their course or after an initial episode of AKI⁴ despite the long duration of neonatal hospitalizations.

To improve our understanding of the importance of late onset AKI, we evaluated the AWAKEN dataset. The primary goals of the current study were to assess the short-term outcomes (including mortality and length of stay) associated with late AKI (defined as occurring >7 days after birth). In addition, we aimed to identify the antenatal, perinatal, and postnatal risk factors for developing late AKI and the gestational age-specific risk factors for the development of late AKI.

MATERIALS AND METHODS

The AWAKEN study methodology along with a comprehensive description of the 24 participating sites has been published.¹ The University of Alabama at Birmingham Institutional Review Board (IRB) approved this collaborative study, and each center received approval from their respective IRBs. The study was registered at ClinicalTrials.gov NCT02443389.

Setting and participants

The AWAKEN study was a 3-month retrospective cohort study of patients admitted to a participating NICU between 1 January and

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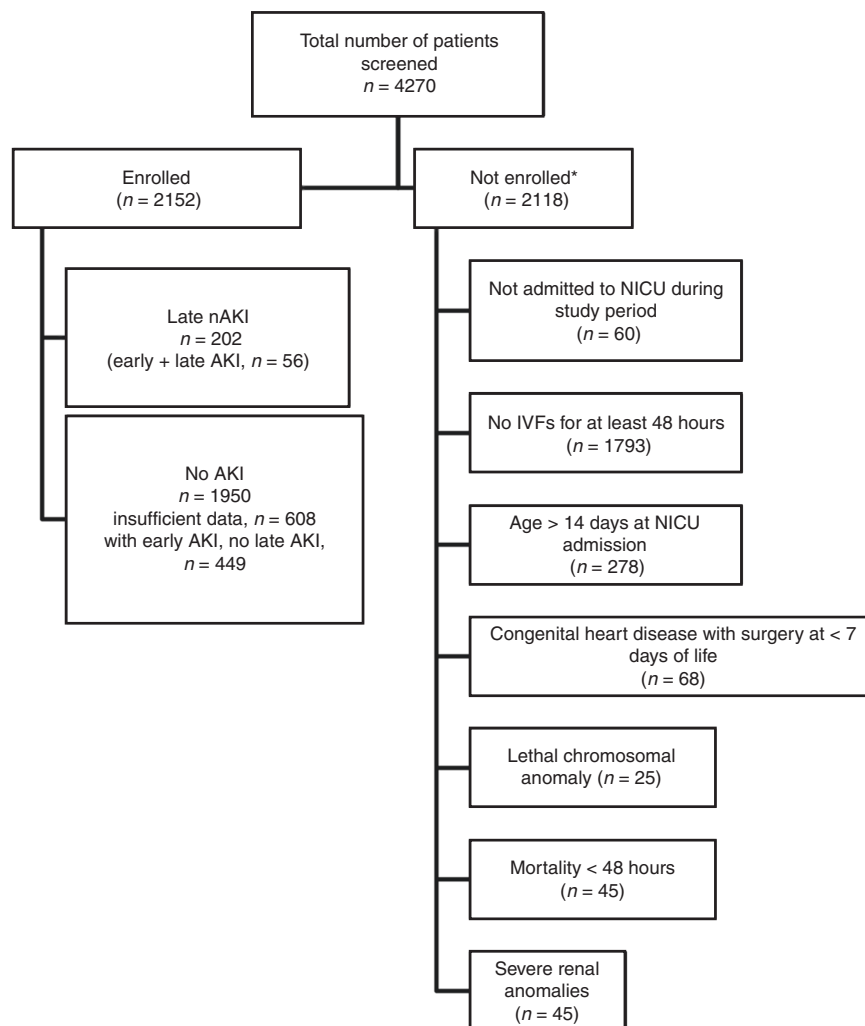


Fig. 1 Participant flow diagram in late AKI: screening and enrollment. Late AKI was defined as occurring after 7 days after birth using serum creatinine data alone. The No AKI group included those with early AKI but not late AKI and those with insufficient data to diagnose AKI. * Subjects could be excluded for multiple reasons

31 March 2014. Data collection began at admission and completed at discharge, death, or 120 days after birth. Figure 1 illustrates the inclusion and exclusion criteria for this study with a final sample of 2152. The outcomes of interest included death, length of stay, and AKI.

Neonatal AKI definition

Late AKI was defined according to the modified Kidney Disease: Improving Global Outcomes workgroup AKI definition using serum creatinine alone⁵⁻⁸ (Supplemental Table S1) and occurring >7 days after birth. The control population included those¹ without the diagnosis of AKI ($n = 1095$),² with early AKI without late AKI ($n = 449$) and⁴ with <2 creatinines after 1 week ($n = 608$). We compared each patient's creatinine measurement to the lowest prior serum creatinine and the maximum stage of AKI was used in the analysis. For subjects with early AKI, recovery from the initial episode of AKI was assessed and new creatinine baseline was used in determination of late AKI. All serum creatinine values were ordered by the clinician as per institutional and clinician practice and collected from the medical record.

Data collection

We extracted variables according to their relevance to AKI. All data including admission and discharge diagnoses definitions reflect

local practice defined by literature-based definitions.¹ Weekly details were collected regarding fluid requirements, electrolytes, blood pressure, and medications. Laboratory monitoring was center-dependent. The data were entered and stored in MediData Rave™, a web-based database housed at Cincinnati Children's Hospital Medical Center. All admission diagnoses preceded the AKI event, whereas the temporal relationship between the discharge diagnoses to the AKI event was unknown (Supplemental Table S2). Congenital renal anomalies were stratified into mild-to-moderate or severe (Supplemental Table S3). Medications were grouped into the following categories: antimicrobials, methylxanthines, diuretics, vasopressors, and non-steroidal anti-inflammatory drugs (NSAIDs) (Supplemental Table S4). Medication exposure was collected weekly and defined as the number of weeks of each medication class administered prior to the AKI event.

Statistical methods

The categorical variables were analyzed by proportional differences; χ^2 test or Fisher exact test. The non-parametric continuous variables were assessed by Wilcoxon Rank Sum tests (median and interquartile ranges). Continuous variables normally distributed were analyzed using t -tests (means and standard deviations).

Table 1. Demographics of the whole cohort and for gestational age cohorts

	Whole cohort (n = 2152)		22–28 weeks (n = 275)		29–35 weeks (n = 954)		≥36 weeks (n = 923)	
	AKI (n = 202)	No AKI (n = 1950)	AKI (n = 195)	No AKI (n = 80)	AKI (n = 51)	No AKI (n = 903)	AKI (n = 71)	No AKI (n = 852)
Gestational age (wks)	31.4 ± 5.9	34.4 ± 4.2	25.0 ± 1.5	26.0 ± 1.6	32.3 ± 2.1	32.5 ± 1.8	38.1 ± 1.5	38.2 ± 1.5
Birth weight (g)	1834 ± 1155	2343 ± 966	775 ± 186	909 ± 261	1746 ± 721	1906 ± 583	3099 ± 708	3136 ± 678
Sex (male)	105 (52%)	1119 (57%)	47 (59%)	110 (56%)	19 (37%)	509 (56%)	39 (55%)	500 (59%)
Race (Caucasian)	119 (59%)	1086 (56%)	35 (44%)	93 (48%)	35 (69%)	504 (56%)	49 (69%)	489 (57%)
Ethnicity (Hispanic)	26 (13%)	266 (14%)	9 (11%)	18 (9%)	10 (20%)	131 (15%)	7 (10%)	117 (14%)
Apgar-1	5 (2, 8)	7 (4, 8)	4 (1, 6)	4 (2, 6)	6 (3, 8)	7 (5, 8)	7 (4, 8)	8 (5, 9)
Apgar-5	7 (6, 8)	8 (7, 9)	7 (4, 8)	7 (5, 8)	8 (6, 9)	8 (8, 9)	8 (6, 9)	9 (7, 9)
Anti-microbials	181 (90%)	1492 (77%)	76 (95%)	188 (96%)	46 (90%)	686 (76%)	59 (83%)	618 (73%)
Methylxanthines	109 (54%)	511 (26%)	74 (93%)	184 (94%)	22 (43%)	305 (34%)	13 (18%)	22 (3%)
Diuretics	78 (39%)	195 (10%)	30 (38%)	75 (39%)	14 (27%)	51 (6%)	34 (48%)	69 (8%)
Vasopressors	70 (35%)	193 (10%)	31 (39%)	53 (27%)	12 (24%)	52 (6%)	27 (38%)	88 (10%)
NSAIDs	47 (23%)	78 (4%)	42 (53%)	68 (35%)	4 (8%)	7 (0.8%)	1 (1%)	3 (0.4%)
Mortality n, (%)	30 (15%)	51 (3%)	18 (22.5%)	21 (10.8%)	6 (11.8%)	13 (1.4%)	6 (8.4%)	17 (2.0%)
LOS (days)	75.1 ± 57.4	26.2 ± 26.5	95.6 ± 53.7	74.8 ± 37.8	73.6 ± 72.7	26.8 ± 19.6	53.2 ± 38.4	14.3 ± 14.0

The association of late AKI and death within the entire cohort was measured by a logistic regression analysis and was conducted to calculate the odds ratio (ORs) and 95% CI. With the limited number of deaths, the following variables were selected to be included in the model: late AKI, gestational age, mode of delivery, 1-min Apgar, admission for hypoglycemia, inborn errors, congenital heart disease, necrotizing enterocolitis, hypoxic ischemic encephalopathy/seizures, exposure to vasopressors, and NSAIDs. The association between late AKI and length of stay was determined in the whole group and the gestational age strata, linear regression was used to calculate crude parameter estimates and 95% CI. Regression models used a backwards procedure with a significance level of <0.2 of stay. A time-to-event analysis for survival with Kaplan–Meier was used to examine the association of mortality and length of stay with AKI severity in the entire cohort and for each gestational age category with a $p < 0.05$ considered to be significant.

A generalized estimating equation (GEE) logistic model accounting for clustering by study center was used to estimate the potential risk factors for late AKI (ORs and associated 95% CIs). Models were created for maternal, neonatal, and medication characteristics. Within each analysis, the following were estimated: 1) crude ORs, 2) adjusted to age, ethnicity, and both Apgar scores at 1 and 5 min and then 3) fully adjusted (i.e., for age, ethnicity, and Apgar-1 and 5 in addition to the other variables of interest). In a supplemental analysis, the maternal, neonatal, and medication characteristic variables were considered for inclusion into a single GEE logistic regression model. The most parsimonious model was chosen using a stepwise selection with a model α -level threshold of <0.10 for entry into the model and of 0.10 for remaining in the model. Models were created for the overall study population and for each of the gestational age cohorts. Pearson's correlation was used to assess the strength of association between median serum creatinine counts and late AKI prevalence by institution.

RESULTS

Demographics

Of the 4270 neonates screened, 2152 were included in the analysis (Fig. 1). The cohort was stratified into 3 gestational age strata: 22–28 weeks ($n = 275$), 29–35 weeks ($n = 954$), ≥36 weeks ($n = 923$). These strata were chosen to maximize sample size, while maintaining clinical relevance and matched the stratification of other AWAKEN analysis. Demographics of the entire cohort and each gestational age category are presented in Table 1.

Late neonatal acute kidney injury

Late AKI occurred in 202/2152 (9%) of the included cohort. Late AKI occurred at a median of 17 days (IQR: 12–32 days) after birth. Within the group who had late AKI, 56/202 (28%) had an early episode of AKI (<7 days) and 24/202 (12%) had >2 episodes of AKI (range: 2–4). The proportion of stage of AKI was consistent within the entire cohort and within the different gestational age cohorts (Supplemental Table S1). The mortality rates between those who had both early and late AKI [12/56 (21%)] were not statistically different than those who had only 1 episode of late AKI [26/178 (15%)] $p = 0.22$. The average time from early to sentinel late AKI was 37.8 ± 29.4 days. The prevalence of late AKI within each gestational age strata was 29% ($n = 80$) in 22–28-week group, 5% ($n = 51$) in the 29–35-week group, and 8% ($n = 71$) in the ≥36 week group ($p < 0.001$).

Outcomes: mortality and length of stay

Compared to neonates without late AKI, mortality was higher in the neonates with late AKI in the whole cohort and each gestational age strata. Late AKI was significantly associated with increased mortality in the crude (OR:6.5 (4.0–10.5), $p < 0.0001$) and adjusted models (aOR:2.1 (1.1–4.0), $p = 0.02$) for the whole cohort (Table 2). The results did not substantially change when the neonates with insufficient data to diagnose AKI were excluded (Table 2). Gestational age models were not constructed due to the low number of death events within each strata. The more severe stages of late AKI were associated with increased mortality (Fig. 2). Neonates with late AKI had longer length of stay than those without AKI in both the crude (49.0 (44.5–53.4), $p < 0.0001$) and adjusted (21.9 (18.2–25.7), $p = 0.02$) models (Table 2). This finding was consistent across all gestational age strata.

Risk factors for late AKI

The risk factors associated with an adjusted odds for late neonatal AKI are summarized in Fig. 3. The adjusted odds to develop late neonatal AKI was analyzed for maternal (Table 3, Supplemental Table S5), neonatal (Table 4) and medications/institutional level (Table 5) exposures. Prevalence of late AKI and median serum creatinine counts was variable across country and type of institution (Supplemental Table S6). In the whole groups intubation, oligo- and polyhydramnios, mild-to-moderate renal anomalies, admission diagnoses of congenital heart disease, necrotizing enterocolitis, and surgical need, were all neonatal factors associated with an increased odds of developing late AKI. Discharge diagnoses of patent ductus arteriosus, necrotizing enterocolitis, sepsis, and urinary tract infection were also associated with an increased odds of late AKI. Medication

Table 2. Prediction models for the association of late AKI with short-term clinical outcomes

Mortality	Crude OR	<i>p</i> -value	Adjusted OR ^a	<i>p</i> -value
Whole cohort (include those with insufficient data)	6.5 (4.0–10.5)	<0.0001	2.1 (1.1–4.0) ^a	0.02
Whole cohort (exclude those without insufficient data)	5.15 (3.15–8.40)	<0.0001	2.17 (1.15–4.10) ^a	0.02

Length of stay (days)	Parameter estimate	<i>p</i> -value	Parameter ^b	<i>p</i> -value
Whole cohort	49.0 (44.5–53.4)	<0.0001	21.9 (18.2–25.7)	<0.0001
22–28 weeks	20.8 (9.5–32.0)	0.0003	15.9 (4.8–27.0)	0.005
29–35 weeks	46.8 (39.7–53.9)	<0.0001	29.7 (22.7–36.7)	<0.0001
≥36 weeks	38.9 (34.7–43.0)	<0.0001	27.5 (23.1–31.9)	<0.0001

^aRegression models predicting mortality adjusted for late AKI, gestational age, 1-minute Apgar, Mode of Delivery, admission for hypoglycemia, inborn errors, congenital heart disease, necrotizing enterocolitis, exposure to vasopressors, NSAIDs, discharge diagnosis of hypoxic encephalopathy/seizures

^bLinear regression adjusted for late AKI, gestational age, 1-minute Apgar, race, intubation, compressions, epinephrine, saline, admission diagnoses: seizures or hypoxic encephalopathy, necrotizing enterocolitis, omphalocele, large for gestational age, congenital renal abnormalities, maternal NSAIDs, discharge diagnoses: with patent ductus arteriosus, systemic hypertension, persistent pulmonary hypertension, bacteremia, urinary tract infections and exposure to nephrotoxic antimicrobial, methylxanthines, diuretics, and NSAIDs

exposures such as diuretics and vasopressors, and NSAIDs were associated with an increased odds of late AKI. The Jaffe reaction was associated with an increased odds of late AKI.

Necrotizing enterocolitis at discharge was associated with increased odds of AKI in both the 22–28 and 29–35 week groups. Oligohydramnios, polyhydramnios and a discharge diagnosis of sepsis increased the odds of AKI in the 29–35-week group. Congenital heart disease, resuscitation with saline, nephrotoxic medications in addition to diuretics and methylxanthine exposure were associated with an increased odds of late AKI in the ≥36-week group.

Several factors were associated with a reduced odds of developing late AKI: steroids for fetal maturity and hypoglycemia (29–35 weeks), maternal hypertension and admission for intraventricular hemorrhage or seizures (≥36 weeks), and early AKI (22–28 and ≥36 weeks).

There was a significant correlation within the individual gestational age cohorts between the median serum creatinine counts and the late AKI prevalence (Fig. 4). The correlation was strongest in the 22–28 week gestational age cohort ($r = 0.58, p < 0.003$).

DISCUSSION

To our knowledge, this is the first dedicated description of AKI occurring after the first week and provides evidence for the association between late neonatal AKI and poor outcomes. The uniqueness of the AWAKEN cohort is not only its large size, but that participants were enrolled across the entire gestational age spectrum, and from multiple centers and countries. Late AKI occurred in 9% of the enrolled or “higher risk” NICU population ($n = 2152$) and 5% total patients admitted to the NICU ($n = 4270$). Importantly, late AKI is independently associated with a 2.1 times higher odds of death and longer hospitalization even after accounting for multiple confounders. Understanding the risk factors and outcomes associated with late AKI can assist clinicians on both an inpatient and outpatient basis. Knowledge of these risk factors can help neonatologists identify those at high risk of AKI and allow nephrologists to distinguish those potentially at highest risk for chronic kidney disease. Finally, for pediatric hospitalists known risk factors may help detect AKI in patients transferred or readmitted from the NICU.

The prevalence of late AKI is greatest in the most preterm infants, 29% in the 22–28-week group. This finding is expected given the longer duration of hospitalization and ongoing exposures in this group. However, many centers in the AWAKEN

study monitored serum creatinine infrequently in the 22–28-week group. Eleven centers had a median serum creatinine count of ≤ 5 following the first postnatal week Supplemental Table S6. This provides further evidence that protocols to screen for AKI should extend past the first week and be initiated during high-risk events, particularly during necrotizing enterocolitis events in the lowest gestational age group. While not reaching statistical significance being small for gestational age was associated with a higher OR for AKI. This in combination with prematurity may be additive risks for AKI, given that being growth restricted is a risk for NEC and other morbidities associated with AKI. Importantly, the combination of growth restriction and AKI may increase risk for CKD in later childhood/adulthood.^{9,10}

In the AWAKEN cohort, a second episode of AKI was not uncommon. In the overall group, nearly 28% ($n = 56$) of patients with late AKI also experienced early AKI. The timing of late AKI was approximately a week later in the group that had a prior episode of early AKI as compared to those without early AKI (median time to late AKI was 23.5 days for those with prior AKI compared to 16 days for those without prior AKI ($p = 0.0002$, Wilcoxon rank sums test)). Although there is a significantly increased odds of late AKI for those with a prior AKI in the crude association, it is probable that the very strong associations of late AKI with necrotizing enterocolitis, congenital heart disease, and surgical need have attenuated the association between early and late AKI in the fully adjusted models. Alternatively, the lack of association in the fully adjusted model may reflect that AKI events are discrete and independent or that late AKI was underdiagnosed due to a lack of standardization of sCr collections, particularly during high risk events. There is little known about the effect of repeated episodes of AKI in neonates. Studies in adults support the detrimental effect of recurrent AKI; both hospitalized adults or adults with diabetes who suffer recurrent AKI demonstrated a doubling of their risk for developing CKD.^{11,12} Unique to neonates, repeated episodes of AKI may be related to decreased available renal reserve with a GFR that does not reach adult levels until 6–12 months of age. Neonatal autopsy studies in preterm neonates show that while postnatal glomerulogenesis continues, the developing glomeruli are morphologically abnormal.¹³ Multiple episodes of AKI may further compromise postnatal glomerulogenesis, resulting in an even lower nephron number.¹⁴

Several maternal factors are notable for their association with a lower risk for late AKI. As with early AKI, multiple gestation was associated with a lower risk for late AKI. Conversely, the receipt of steroids, maternal hypertension, and hypoglycemia were all uniquely associated with a decreased risk for late AKI. Each of

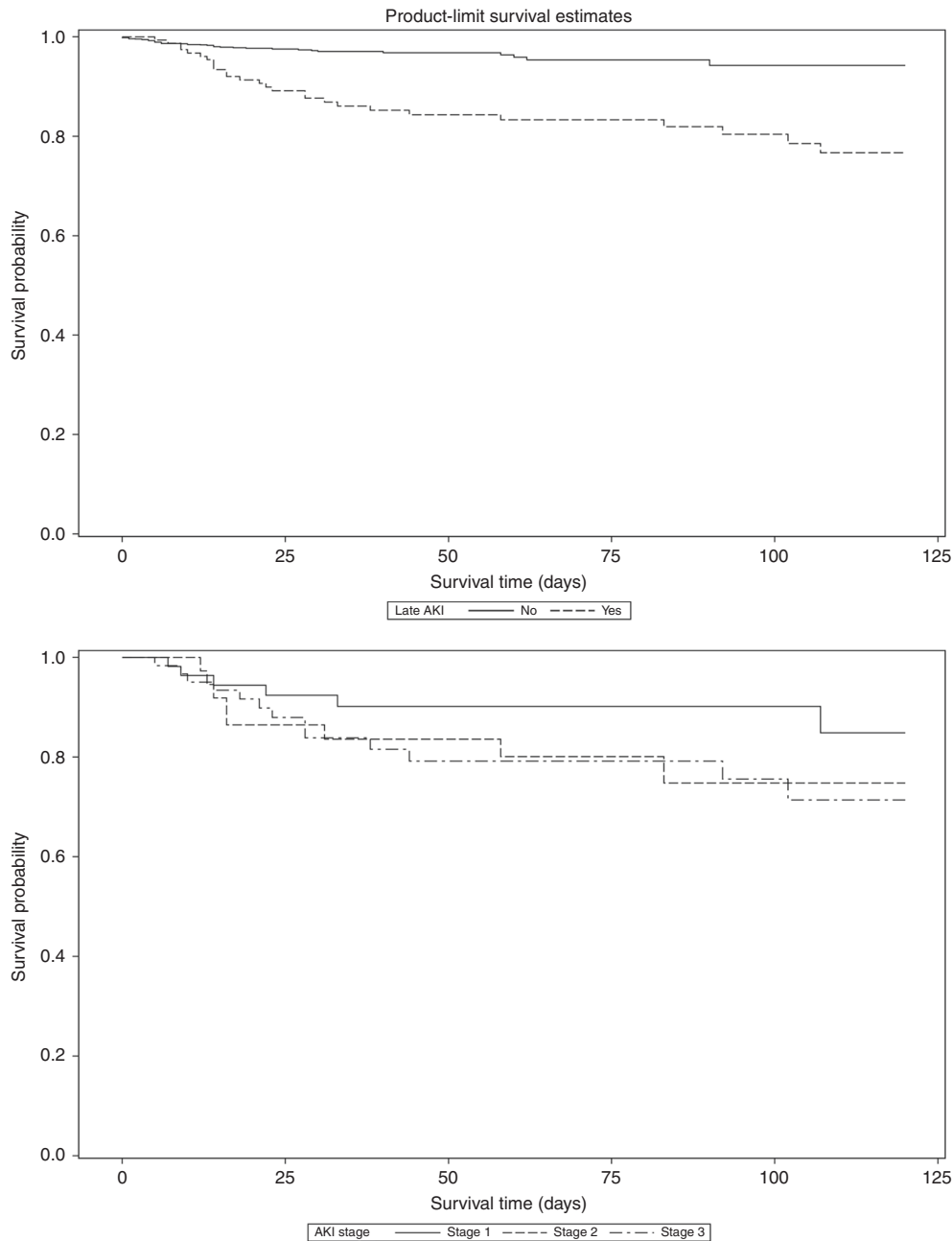


Fig. 2 Survival outcomes in late AKI for the whole cohort and by stages of AKI. Survival curve for late AKI (a) and by stages of AKI (b) in the whole cohort. Survival was lower in the group with late AKI and in highest stages of AKI

these factors represents a setting in which a mother might receive exogenous or endogenous increase in steroids to mature the lungs which may also inturn mature the kidneys.

As perinatal events and interventions determine many of the early AKI risk factors, we speculated that there would be unique factors that discriminated those with late AKI. Several unique perinatal factors were associated with late onset AKI including intubation, oligohydramnios, polyhydramnios and mild-moderate renal anomalies. Late AKI was associated with resuscitation efforts with intubation, potentially highlighting a sicker population of infants. Improvements in perinatal strategies, particularly with the trend toward a trial of early continuous positive airway pressure in lieu of intubation may extend beneficial effects including reduction of AKI.^{15–18} The presence of oligohydramnios and polyhydramnios were both associated with an increased risk of

late AKI. Oligohydramnios may be associated with fetal renal anomalies/dysfunction affecting lung development (potentially necessitating intubation), and polyhydramnios may be associated with gastrointestinal abnormalities that impair swallowing of amniotic fluid. The finding of increased risk of late AKI in the presence of alterations in amniotic fluid volume therefore may be a proxy for fetal conditions such as renal or gastrointestinal abnormalities.

Specific associations between gastrointestinal diseases such as necrotizing enterocolitis and late AKI were detected in this study. The suspicion of necrotizing enterocolitis on admission in the 22–28-week group and discharged with NEC as diagnosis in the 22–35-week group were both associated with an increased risk of late AKI. A recent single-center study of neonates with an average gestational age of 30.8 weeks

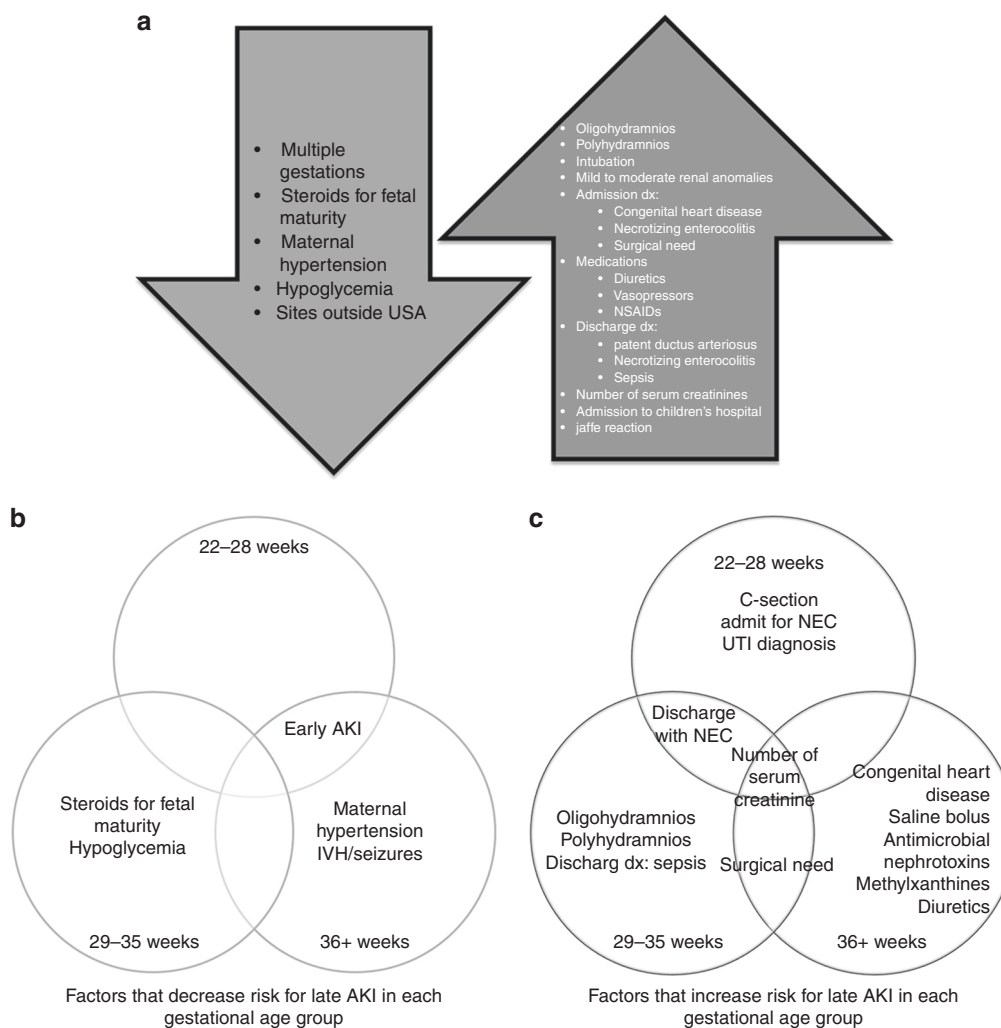


Fig. 3 Perinatal factors that are associated with increased/decreased risk of late acute kidney injury by gestational age group. In **a**, the white arrow contains factors associated with reduced odds and black arrow contains factors associated with increased odds for late AKI. In **b**, the white Venn diagram demonstrates unique and overlapping factors within each of the gestational age cohorts associated with late AKI. The black Venn diagram (**c**) displays those risk factors associated with late AKI

demonstrated a strong association between necrotizing enterocolitis and AKI.¹⁹ Animal models of necrotizing enterocolitis show not only intestinal inflammation, but also a robust kidney inflammatory response with infiltration of mononuclear cells and disruption of the tight junctions within the kidney.²⁰ These findings suggest that the mechanism for AKI following necrotizing enterocolitis may not solely be related to hypoperfusion of the kidney during sepsis, but also to the resultant inflammatory response. Care bundles and exclusive use of human milk feedings along with probiotics aimed at preventing necrotizing enterocolitis may decrease the incidence of late AKI and other associated morbidities.

Several admission and discharge diagnoses were associated with a risk of late AKI including congenital heart disease, surgical need, necrotizing enterocolitis, sepsis, and patent ductus arteriosus. Previous reports have indicated an increased risk of developing AKI after surgical repair of congenital heart disease.^{21,22} Similarly, we observed a 10-fold increase in the risk for developing late AKI in neonates with congenital heart disease. Because of the retrospective nature of our data, we are unable to differentiate between AKI development pre- or post-operatively. Similarly, the AWAKEN dataset did not contain information on the temporal relationship of late AKI and discharge diagnoses such as

necrotizing enterocolitis, and sepsis. The postnatal care of infants with surgical diagnoses, cardiac anomalies, and necrotizing enterocolitis may need to be further refined, with particular attention paid to fluid management, practice guidelines for the early and routine monitoring of serial creatinine and glomerular filtration rate measurements, and early involvement of nephrology in the management of AKI.

A number of medications were associated with increased risk of late AKI including diuretics (fully adjusted OR 2.38), vasopressors (fully adjusted OR 2.42) and NSAID's (fully adjusted OR 2.68). This demonstrates the importance of attention to medications and their potential cumulative effects, supporting programs such as NINJA²³ to minimize those risks. The cumulative exposure of nephrotoxins, including NSAIDs, may influence the development of late AKI. This is supported by the animal data that shows prenatal exposure to indomethacin results in reduce nephron number²⁴ and an increase of urinary podocytes in indomethacin-treated neonates.²⁵

Despite the strengths of this study, AWAKEN has several limitations. One important limitation is the variability in the method and the frequency of creatinine measurements between institutions. We have demonstrated that late AKI prevalence correlates with the number of creatinines measured in the

Table 3. Odds ratios^a (ORs) and 95% confidence intervals (CIs) for the association between maternal conditions and fetal exposures associated with late AKI in the overall cohort

	Crude OR (95% CI)	Age, Ethnicity, and Apgar-1 and 5-adjusted OR (95% CI)	<i>p</i> -value	Fully adjusted ^b OR (95% CI)	<i>p</i> -value
Multiple gestations	0.70 (0.46–1.09)	0.51 (0.33–0.78)	0.0017	0.52 (0.34–0.80)	0.0027
Steroids for fetal maturation	1.18 (0.68–2.03)	0.51 (0.33–0.81)	0.0038	0.56 (0.34–0.93)	0.0247
Hypertensive disease during pregnancy	0.71 (0.51–0.99)	0.64 (0.43–0.95)	0.0269	0.64 (0.45–0.92)	0.0169
Amniotic fluid					
Oligohydramnios	2.01 (1.20–3.37)	2.13 (1.21–3.76)	0.0087	2.38 (1.35–4.18)	0.0027
Polyhydramnios	2.47 (1.48–4.11)	3.38 (1.87–6.10)	<.0001	3.80 (2.12–6.79)	<0.0001
Normal	Ref	Ref	—	Ref	—
Mode of delivery					
C-section, scheduled	0.67 (0.33–1.33)	0.83 (0.42–1.66)	0.6052	0.93 (0.44–1.92)	0.8353
C-section, unscheduled	1.00 (0.71–1.41)	0.68 (0.50–0.93)	0.0146	0.82 (0.60–1.12)	0.2111
Vaginal delivery	Ref	Ref	—	Ref	—
Meconium exposure	0.67 (0.38–1.18)	1.00 (0.55–1.83)	0.9956	1.07 (0.58–1.98)	0.8274

^aEstimated from a generalized estimating equation (GEE) logistic model accounting for clustering by study center^bAdjusted for gestational age, ethnicity, Apgar-1 and 5 in addition to other variables in the table**Table 4.** Odds ratios^a (ORs) and 95% confidence intervals (CIs) for the association between neonatal conditions and exposures associated with late AKI in the overall cohort

	Crude OR (95% CI)	Age, Ethnicity, and Apgar-1 and 5-adjusted OR (95% CI)	<i>p</i> -value	Fully adjusted ^b OR (95% CI)	<i>p</i> -value
Outborn	1.25 (0.59–2.64)	1.48 (0.72–3.03)	0.2830	1.08 (0.48–2.39)	0.8575
Size					
Small for gestational age	1.06 (0.68–1.67)	1.40 (0.89–2.21)	0.1466	1.38 (0.90–2.11)	0.1384
Normal for gestational age	Ref	Ref	—	Ref	—
Large for gestational age	0.84 (0.44–1.61)	1.44 (0.84–2.47)	0.1819	1.55 (0.80–2.99)	0.193
Intubation	4.54 (2.96–6.97)	2.98 (1.94–4.56)	<.0001	2.71 (1.77–4.17)	<.0001
Chest compressions	2.47 (1.39–4.38)	0.89 (0.51–1.55)	0.689	0.96 (0.48–1.93)	0.9056
Epinephrine	2.40 (1.17–4.90)	0.83 (0.31–2.24)	0.709	0.58 (0.19–1.76)	0.3389
Saline bolus	1.82 (1.27–2.61)	1.14 (0.75–1.73)	0.546	1.11 (0.60–2.07)	0.7335
Hypoxic ischemic encephalopathy/seizures	0.77 (0.39–1.52)	0.54 (0.21–1.38)	0.196	0.80 (0.34–1.88)	0.6108
Hypoglycemia	0.43 (0.22–0.86)	0.51 (0.26–1.01)	0.054	0.46 (0.22–0.97)	0.0401
Hyperbilirubinemia	1.13 (0.42–3.05)	1.04 (0.51–2.14)	0.917	0.99 (0.39–2.53)	0.9786
Inborn errors (metabolism)	1.71 (0.55–5.34)	0.59 (0.05–7.46)	0.685	0.23 (0.00–23.14)	0.5344
Congenital heart disease	4.90 (3.12–7.70)	10.15 (4.93–20.93)	<.0001	9.29 (4.41–19.58)	<.0001
Admitted for necrotizing enterocolitis	25.99 (12.43–54.35)	18.37 (9.93–33.97)	<.0001	19.00 (6.91–52.24)	<.0001
Surgical need	3.14 (1.68–5.87)	6.17 (2.62–14.53)	<.0001	5.80 (2.75–12.22)	<.0001
Mild-moderate kidney anomalies	5.03 (2.82–8.95)	4.70 (2.56–8.62)	<.0001	2.58 (1.22–5.45)	0.0128
Discharge diagnosis of PDA	4.03 (2.38–6.82)	2.57 (1.56–4.25)	0.0002	1.73 (1.03–2.91)	0.0382
Discharge diagnosis of IVH	4.08 (2.47–6.72)	1.78 (1.11–2.84)	0.0166	1.27 (0.75–2.16)	0.3748
Discharge diagnosis of NEC	7.17 (3.45–14.89)	4.14 (2.04–8.43)	<.0001	4.10 (1.79–9.37)	0.0008
Discharge diagnosis of UTI	4.97 (2.67–9.23)	2.96 (1.38–6.36)	0.0054	1.20 (0.67–2.15)	0.5442
Discharge diagnosis of sepsis	3.14 (2.11–4.67)	2.47 (1.54–3.95)	0.0002	1.85 (1.16–2.95)	0.0095
AKI < 7 days	1.52 (1.09–2.12)	1.39 (0.99–1.96)	0.0535	1.10 (0.71–1.69)	0.6688

^aEstimated from a generalized estimating equation (GEE) logistic model accounting for clustering by study center^bAdjusted for gestational age, ethnicity, Apgar-1 and 5 in addition to other variables in the table

22–28-week group; therefore, kidney injury may have been under-reported due to infrequent serum creatinine monitoring (Fig. 4). Of the 2152 enrolled, 608 participants had <2 creatinine measurements and were classified as no AKI based on sensitivity

analysis. However, the risk for bias is prominent and this study therefore highlights the need to standardize monitoring practices in the NICU. These renal screening protocols should be based on specific risk factors providing meaningful information for the most

Table 5. Odds ratios^a (ORs) and 95% confidence intervals (CIs) for the association between medications, types of institutions, and creatinine method associated with late AKI in the overall cohort

	Crude OR (95% CI)	Age, Ethnicity, and Apgar-1 and 5-adjusted OR (95% CI)	p-value	Fully adjusted ^b OR (95% CI)	p-value
Anti-microbial medications (y/n) ^c	2.65 (1.53–4.58)	1.97 (1.26–3.08)	0.0031	1.38 (0.87–2.19)	0.1766
Methylxanthines (y/n) ^c	3.30 (1.98–5.49)	1.70 (0.90–3.24)	0.1034	1.61 (0.79–3.28)	0.1885
Diuretics (y/n) ^c	5.66 (3.71–8.64)	3.69 (2.27–5.99)	<.0001	2.38 (1.37–4.12)	0.0020
Vasopressors (y/n) ^c	4.81 (3.22–7.19)	3.46 (2.13–5.64)	<.0001	2.42 (1.36–4.30)	0.0025
NSAIDs (y/n) ^c	7.28 (3.91–13.55)	3.48 (1.85–6.58)	0.0001	2.68 (1.25–5.77)	0.0114
Serum creatinine number	1.20 (1.13–1.28)	2.23 (1.15–1.31)	<0.0001	1.17 (1.09–1.25)	<.0001
Site type					
Children's hospital	2.00 (0.84–4.75)	2.29 (0.95–5.53)	0.0642	1.99 (1.06–3.75)	0.0318
Perinatal	0.84 (0.38–1.84)	0.87 (0.48–1.60)	0.6599	0.96 (0.59–1.55)	0.8623
Perinatal/Surgical	Ref	Ref	—	Ref	—
Jaffe reaction	1.71 (0.76–3.84)	1.86 (0.80–4.33)	0.1496	2.47 (1.49–4.09)	0.0005
Sites outside of the USA	0.23 (0.11–0.48)	0.19 (0.08–0.45)	0.0002	0.13 (0.03–0.59)	0.0082

Anti-microbial medications: acyclovir, amphotericin B, aminoglycosides, piperacillin-tazobactam and vancomycin; methylxanthine medications: caffeine and theophylline; diuretic medications: bumetanide, chlorothiazide, furosemide, and spironolactone; vasopressor medications: dobutamine, epinephrine, milrinone, norepinephrine, and dopamine; and NSAID medications: indomethacin and ibuprofen

^aEstimated from a generalized estimating equation (GEE) logistic model accounting for clustering by study center

^bAdjusted for gestational age, ethnicity, Apgar-1 and 5 in addition to other variables in the table

^cAll medications were given prior to the episode of AKI.

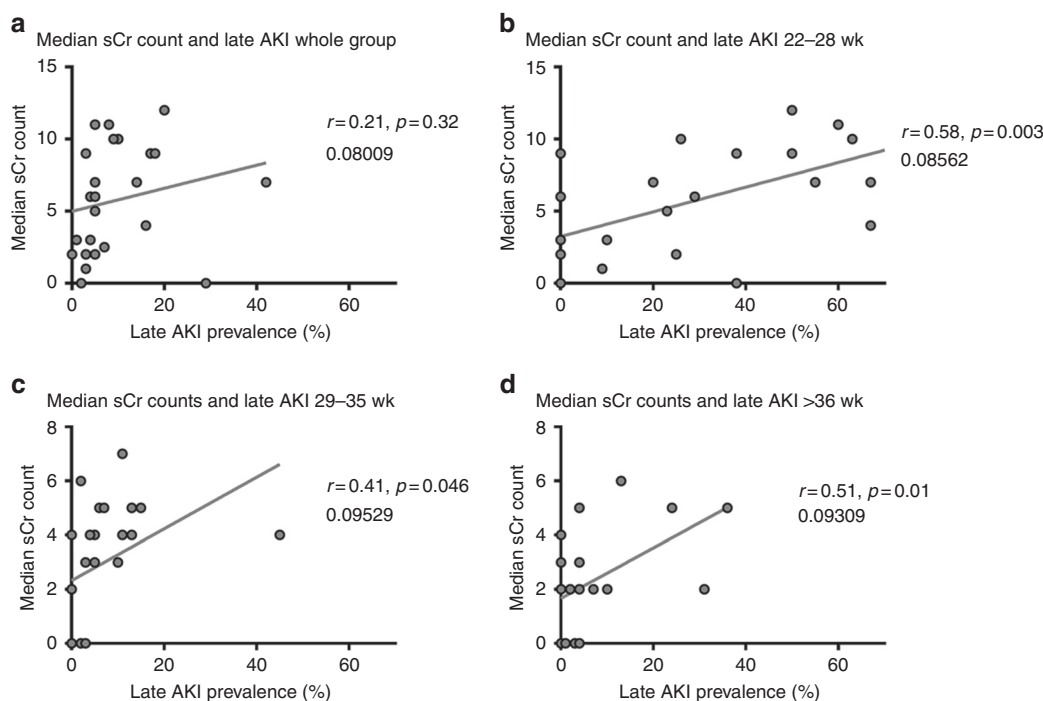


Fig. 4 Relationship between late AKI prevalence and serum creatinine monitoring for the whole cohort and by gestational age group. Correlation between prevalence of late AKI at each individual study site and frequency of serum creatinine monitoring, represented by the median number of creatinine counts: whole group (a), 22–28 wk group (b), 29–35 wk group (c), and ≥ 36 wk group (d). There is a direct relationship between the number of serum creatinines and late AKI prevalence in the youngest gestational age cohort ($r = 0.58, p = 0.003$)

‘at risk’ populations, while limiting cost and negative effects of blood draws in those who have low likelihood to develop AKI. The increased risk of AKI as determined by method of analysis is important to note—as it may denote potential bias or a true increased risk. To better understand the validity of this relationship, we examined the fully adjusted model in Table 5 stratified by Jaffe and enzymatic reactions. There was no difference in the estimated associations between the two reaction types; thus, we

believe any bias through the use of Jaffe would be non-differential and our reported associations are likely underestimates of the true associations. The Jaffe methodology for assessment of creatinine can be affected by bilirubin or other pigmented influences. The different analysis methods and automated analysers produce higher levels of creatinine with the Jaffe method, but this is predominantly at low levels of creatinine.^{26,27} If the definition of AKI was based on a serum creatinine cut off, the association

between late AKI and the Jaffe reaction would be more clear. However the KDIGO definition is based on changes from a baseline, making it important for future prospective studies to take into account laboratory methods for creatinine assessment to fully answer this question. Other limitations of the AWAKEN study are inherent to those related to a retrospective analysis. Data were extracted from all individual institutions electronic medical record or the subject's paper chart. The sources for bias included misclassification bias because there was a potentially greater risk for missing a true AKI event in those participants with fewer measured serum creatinines. Importantly, this analysis did not evaluate all neonates or even all neonates in the NICU, only those who met inclusion criteria. The indications for a number of interventions or therapies were unavailable, the temporal relationship between discharge diagnoses and AKI could not be assessed and our findings for neonates with congenital heart disease are not generalizable as only those with surgery performed >7 days after birth were included. These details are important in designing future prospective studies as data extraction from the subject's chart might have inherent accuracy issues.²⁸

In conclusion, late AKI is independently associated with a 2.1 times odds of death and longer hospitalization with worse outcomes when stratified by severity of AKI. The prevalence of AKI may be even higher due to the variability in frequency of creatinine measurements, and is an important factor for care providers to consider in caring for neonates in the NICU, as well as in planning future research. Care providers should be aware that in addition to a lower gestation age and Apgar scores, intubation, polyhydramnios, oligohydramnios, any renal anomalies, congenital heart disease, surgical need, necrotizing enterocolitis, sepsis, patent ductus arteriosus, and urinary tract infections are all independently associated with late AKI. Importantly, nearly one third of neonates with late AKI had an episode of early AKI, potentially increasing the risk for long-term chronic kidney disease. Although it is challenging to study the long-term kidney impact of AKI, research in this area should be a priority given the prevalence of AKI and potential consequence of CKD.

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AUTHOR CONTRIBUTIONS

J.R.C. and A.L.K. contributed to the conceptualization and design of the study, collected data, aided the data analysis, and drafted the initial manuscript. L.B. and R.G. completed the data analysis and interpretation, contributed to the drafting and revising the manuscript. D.A. contributed to the conceptualization and design of the study, aided in data analysis, and contributed to the revising of the manuscript for critically important intellectual content. P.D.B., M.F., J.G., S.H., S.I., A.M., R.K.O., S.R., C.J.R., M.R., S.S., and M.S. contributed to the study design, collecting or supervising the collection of data, and revising the manuscript for critically important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ADDITIONAL INFORMATION

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