



# Acute kidney injury in neonatal encephalopathy: an evaluation of the AWAKEN database

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## Abstract

**Background** Acute kidney injury (AKI) is common in neonatal encephalopathy (NE) and is associated with worse outcomes. Our objectives were to determine the incidence, risk factors, and outcomes of AKI in infants with NE.

**Methods** We performed a retrospective analysis of infants  $\geq 34$  weeks' gestational age with a diagnosis of NE from the Analysis of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) database. AKI was defined using the modified Kidney Disease Improving Global Outcomes criteria. Perinatal and postnatal factors were evaluated. Multivariate logistic and linear regressions were performed.

**Results** One hundred and thirteen patients with NE were included. 41.6% (47) developed AKI. Being born outside the admitting institution (OR 4.3; 95% CI 1.2–14.8;  $p = 0.02$ ), intrauterine growth restriction (OR 10.3, 95% CI 1.1–100.5;  $p = 0.04$ ), and meconium at delivery (OR 2.8, 95% CI 1.04–7.7;  $p = 0.04$ ) conferred increased odds of AKI. After controlling for confounders, infants with AKI stayed in the hospital an average of 8.5 days longer than infants without AKI (95% CI 0.79–16.2 days;  $p = 0.03$ ).

**Conclusions** In this multi-national analysis, several important perinatal factors were associated with AKI and infants with both NE and AKI had longer length of stay than NE alone. Future research aimed at early AKI detection, renoprotective management strategies, and understanding the long-term renal consequences is warranted in this high-risk group of patients.

**Keywords** Neonate · Acute kidney injury · Neonatal encephalopathy · Hypoxic-ischemic encephalopathy

## Introduction

Neonatal encephalopathy (NE), as a consequence of perinatal asphyxia, occurs in 2–5 per 1000 live births and remains a major cause of morbidity and mortality in term infants [1]. Neonatal acute kidney injury (AKI) occurs frequently in infants with NE [2] and is an independent risk factor for poor neurodevelopmental outcome and mortality [3, 4]. Additionally, neonates who survive even a transient episode of AKI in infancy are at increased risk for long-term chronic kidney disease [5]. Various therapies routinely used in the management of NE (including aggressive fluid restriction, reliance on parenteral nutrition, and antibiotic use) may pose additional risk to the kidneys. Thus, the primary episode of asphyxia and its subsequent treatment may exacerbate AKI in infants with NE, placing them at additional short- and long-term risk to develop poor outcomes.

The modified Kidney Disease: Improving Global Outcomes (KDIGO) criteria classify neonatal AKI as stage I,

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II, or III based on increases in serum creatinine (SCr) from baseline and/or decrease in urine output [6]. To date, no multicenter studies have determined the incidence of AKI in asphyxiated infants using this definition. In certain high-risk neonatal populations (premature infants, very low birth weight (VLBW)/extremely low birth weight (ELBW) infants, and infants with sepsis), low Apgar scores, hypotension, non-steroidal anti-inflammatory drugs (NSAIDs), and antibiotic exposure are among the factors known to increase the risk of AKI [6]. However, antenatal risk factors that increase the likelihood of AKI among asphyxiated infants have not been well described.

We used the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) database to (1) determine the incidence of AKI (using the modified KDIGO definition) among infants with NE, (2) compare the maternal and infant risk factors associated with AKI among infants with and without neonatal encephalopathy, and (3) determine the independent association of AKI on length of stay, mortality, and respiratory support among infants with NE.

## Methods

**Study design and data source** The AWAKEN study is the collaborative effort of 24 level III/IV neonatal intensive care units (NICUs) that comprise the Neonatal Kidney Collaborative (NKC) [6]. The AWAKEN database was designed to describe the epidemiology, validate the definition, and identify risk factors for neonatal AKI. Infants admitted to the NICU between January 1 and March 31, 2014 were included in AWAKEN if they met prespecified inclusion/exclusion criteria. The main inclusion criterion was receipt of intravenous fluids for at least 48 h. Patients excluded from AWAKEN included infants > 14 days of age at admission, those with congenital heart disease requiring surgery within the first week of life, those with lethal chromosomal anomalies, and infants who died within 48 h of delivery. Details on the other criteria and specifics of the NKC and the database, which includes 325 unique variables including demographics, physiologic parameters, creatinine values, and discharge characteristics, have been previously published [7]. Additionally, our analysis excluded infants with severe congenital anomalies of the kidney and urinary tract (CAKUT) (including bilateral grade IV–V vesicoureteral reflux, bilateral moderate-severe hydronephrosis, bilateral hypoplasia/dysplasia, and either autosomal dominant or recessive polycystic kidney disease), and infants born < 34 weeks GA.

**Study population** This retrospective cohort study included infants from the AWAKEN dataset  $\geq 34$  weeks' gestational age (GA) who had an admission or discharge diagnosis of

NE. Younger infants were excluded, as NE is not generally the primary admitting diagnosis for premature infants. Variables were predetermined based on their clinical relevance to neonatal AKI and/or NE.

**Variable definitions** AKI was defined by the KDIGO workgroup definition modified for neonates: any rise in SCr of 0.3 mg/dL or 50% from the lowest previous value and/or urine output of < 1 mL/kg/h averaged over 24 h on postnatal days 2–7 [8]. Delivery room resuscitation data was captured by four variables describing respiratory support alone (mask or blow-by oxygen, continuous positive airway pressure, positive pressure ventilation breaths, or intubation), or respiratory support plus chest compressions, and/or epinephrine, and/or normal saline bolus. Deliveries occurring outside the AWAKEN institution (including home births, those occurring at a birth center, or those occurring at a lower acuity referring hospital) were captured as “outborn.” Outcomes of interest included NICU length of stay (in days), death during hospitalization, and duration of respiratory support.

Ventilation support was defined by receipt of noninvasive positive pressure ventilation, invasive conventional ventilation, or high-frequency ventilation. Oxygen support was defined as the receipt of oxygen by hood or nasal cannula. Weekly evaluation of ventilation and oxygen support in the first 4 weeks of life was then calculated. We defined “oxygen-free weeks” as any week in which a subject was alive and not receiving supplemental oxygen or mechanical ventilation. We defined “ventilation-free weeks” as any week in which a subject was alive and either required supplemental oxygen only, or required no respiratory support.

**Statistical analysis** To assess the bivariate association between maternal and infant characteristics and AKI, categorical variables were analyzed by proportional differences with the chi-square or the Fisher exact test (where appropriate). All continuous variables were tested for normality using the Shapiro-Wilk test. For normally distributed continuous variables, the mean  $\pm$  standard deviation (SD) was reported and analyzed using a Student *t* test. For non-normally distributed variables, the median and interquartile ranges (IQR) were reported, and groups were compared using the Wilcoxon rank-sum test. To assess the independent associations, a forward selection logistic regression process was used with a standard of entry of  $p < 0.2$ . Additionally, intrauterine growth restriction (IUGR), maternal diabetes, hypertensive gestational diseases (maternal hypertension, pre-eclampsia, or eclampsia), and intrapartum nuchal cord complications were prespecified and forced into the model due to the clinically relevant and biological mechanisms of NE and AKI. We also included nephrotoxic drug exposure and fluid overload in the first 7 days, as these are also known risk factors for AKI. Linear regression was used to determine the independent impact of AKI among those with

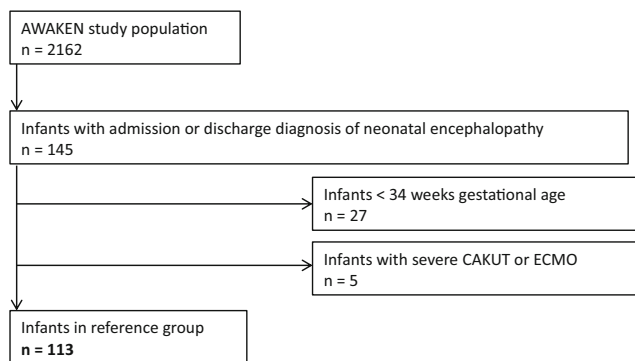
NE on length of stay and was constructed using a backwards selection procedure with a significance level of  $<0.2$ . All analyses were performed using SAS 9.4 software (Copyright © 2012 SAS Institute Inc. Cary, NC, USA).

## Results

There were 2162 infants in the AWAKEN cohort. Figure 1 summarizes the breakdown of patients excluded and used in the final analysis. After excluding patients who did not meet inclusion criteria, 145 had an admission diagnosis of NE. An additional 32 infants were excluded based on prespecified exclusion criteria ( $N=27$  for  $<34$  weeks GA, and  $N=5$  for CAKUT), leaving 113 patients in the final analysis. 70.3% of these infants were admitted to the ICU on day of life 0; 22.9% were admitted on day of life 1. Only one patient was admitted beyond 7 days of age.

The incidence of AKI in the cohort was 41.6% ( $n=47$ ). Of the 47 infants with AKI, 13 (27.7%) had creatinine-defined AKI, 22 (46.8%) had urine output-defined AKI, and 12 (25.5%) met both creatinine and urine output criteria for AKI.

Patient demographics, maternal characteristics, and perinatal patient characteristics are summarized in Table 1. There were no significant differences in race/ethnicity, gestational age at delivery, or birth weight among those with and without AKI. A greater proportion of infants who were outborn developed AKI ( $n=43$ , 91.5%) compared to those who were born at the participating level III/IV NICU ( $n=46$ , 69.7%) ( $p=0.005$ ). The NICU admission temperature was also significantly lower among patients with AKI ( $34.5 \pm 2.2$  °C) compared to patients without AKI ( $35.6 \pm 1.8$  °C) ( $p=0.04$ ). Of the pregnancy characteristics, IUGR was more common in those with AKI, although not statistically significantly ( $p=0.08$ ). Of the intrapartum complications, the presence of meconium-stained amniotic fluid (MSAF) was significantly more common among patients with AKI compared to those



**Fig. 1** Description of study population and the reference group. AWAKEN Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates, CAKUT congenital anomalies of kidney or urinary tract, ECMO extracorporeal membrane oxygenation

without AKI [17/47, 36.2% vs. 12/66, 18.2%;  $p=0.03$ ]. Need for advanced delivery room resuscitation (chest compressions, epinephrine, or volume expansion) and Apgar scores did not differ between those with and without AKI.

We also compared the demographics of all term and near-term infants with AKI, with and without neonatal encephalopathy (Table 2). There were no significant differences in gender, race, ethnicity, pregnancy-related conditions, or mode of delivery. Infants with AKI and NE were more often 37 weeks' or more gestation, were born outside the admitting institution, required more advanced delivery room resuscitation, had lower Apgar scores, and had more intrapartum complications (nuchal cord, MSAF, or shoulder dystocia) than infants with AKI alone. Infants with AKI and NE were more frequently exposed to nephrotoxic drugs and fluid overload.

In the multivariate logistic regression analysis (after adjusting for maternal diabetes, hypertensive diseases of pregnancy, intrapartum nuchal cord complications, nephrotoxic medications, and fluid overload), being outborn, having IUGR, and MSAF were independently associated with AKI. The logistic regression analysis is summarized in Table 3.

There was no difference in mortality rate in those with AKI ( $n=3$ , 6.4%), compared to those without AKI ( $n=5$ , 7.6%) ( $p=1.0$ ). When oxygen-free and ventilator-free weeks were compared, AKI was not associated with a statistically significant difference in degree or duration of respiratory support (Table 4). After controlling for IUGR, maternal diabetes, hypertensive gestational diseases, nuchal cord complications, nephrotoxic medications, and fluid overload, infants with AKI spent 8.5 days longer in the NICU than infants without AKI (95% CI 0.79–16.2,  $p=0.03$ ) (Table 5).

## Discussion

The incidence of AKI among term and near-term neonates with NE in the AWAKEN cohort was 41.6%. This is higher than the overall incidence of AKI (30%) in the entire AWAKEN cohort and higher than the incidence of AKI in the term infants (36.7%) [9]. The diagnosis of AKI was made on the basis of oliguria alone in 48% of the NE cohort. This likely reflects that careful assessment of urine output is part of routine clinical practice in the management of encephalopathic term infants, while frequent serum creatinine monitoring is less common.

We found that being born outside the NKC-affiliated hospital had 4.3 times the odds of developing AKI. We hypothesize this relationship is multifactorial and may be due at least in part to differences in care at large referral institutions and differences in the disease severity for those transferred to a higher level of care. Having MSAF also increased odds of AKI. MSAF is thought to indicate a state of intrauterine stress and hypoxia, which could lead to increased vulnerability of

**Table 1** Patient demographics and maternal, perinatal, and postnatal characteristics

	NE; no AKI ( <i>n</i> = 66)	NE ± AKI ( <i>n</i> = 47)	<i>p</i> value
Gender (male)	44 (66.7%)	23 (48.9%)	0.06
Ethnicity			1.00
Hispanic	4 (8.2%)	3 (8.8%)	
Non-Hispanic	45 (91.8%)	31 (91.2%)	
Race			0.50
White	33 (50%)	26 (55.3%)	
Black	11 (16.7%)	10 (21.3%)	
Other	22 (33.3%)	11 (23.4%)	
Gestational age (weeks)			0.64
34–37	14 (21.2%)	8 (17%)	
37 or greater	52 (78.8%)	39 (83.0%)	
Birthweight (g)			0.55
1501–2501	9 (13.6%)	4 (8.7%)	
≥ 2501	57 (86.4%)	42 (91.3%)	
Day of life at admission	0 (0, 0)	0 (0, 1)	0.10
Outborn*	46 (69.7%)	43 (91.5%)	0.005
Mode of delivery			0.26
Cesarean section	34 (54.0%)	18 (42.9%)	
Vaginal birth	29 (46.0%)	24 (57.1%)	
Delivery room resuscitation			
Respiratory support	65 (98.5%)	43 (91.5%)	0.07
Chest compressions	16 (24.2%)	13 (27.7%)	0.68
Epinephrine	8 (12.1%)	9 (19.1%)	0.30
Normal saline bolus	12 (18.2%)	13 (27.7%)	0.23
Admission temp. (°C)	35.6 ± 1.8	34.5 ± 2.2	0.04
Apgar scores			
1 min	2.0 (1.0, 3.0)	1.5 (1.0, 3.0)	0.43
5 min	4.0 (3.0, 6.0)	4.0 (2.0, 6.0)	0.35
Pregnancy characteristics			
Intrapartum infection	9 (13.6%)	5 (10.6%)	0.77
Diabetes	8 (12.1%)	6 (12.8%)	1.00
Gestational hypertension	8 (12.1%)	4 (8.5%)	0.76
IUGR	1 (1.5%)	5 (10.6%)	0.08
Prenatal tobacco use	8 (12.1%)	2 (4.3%)	0.19
Intrapartum complications			
Nuchal cord	11 (16.7%)	12 (25.5%)	0.34
MSAF	12 (18.2%)	17 (36.2%)	0.03
Severe bleeding	6 (9.1%)	3 (6.4%)	0.73
Shoulder dystocia	4 (6.1%)	3 (6.4%)	1.00
Postpartum factors			
NT drug exposure**	49 (74.2%)	41 (87.2%)	0.10
Fluid overload <sup>†</sup>	22 (33.3%)	23 (48.9%)	0.12
Bacteremia/meningitis <sup>‡</sup>	2 (3%)	1 (2%)	1.00

Data are *n* (%), mean (SD), or median (IQR 25, 75)

\*Outborn indicates infant born outside the admitting NICU (including home births, birth centers, and lower-acuity facilities)

\*\*NT drug exposure means nephrotoxic drug exposure within first 7 days (gentamicin, vancomycin, furosemide, indomethacin)

<sup>†</sup>Fluid overload defined as weight > 5% above birth weight at any point in the first 7 days of life

<sup>‡</sup>Culture-positive bacteremia or meningitis within the first 7 days of life

AKI acute kidney injury, *g* grams, °C degrees celsius, IUGR intrauterine growth restriction, MSAF meconium-stained amniotic fluid

the kidneys. Similarly, the finding that IUGR also increased an infant's odds of developing AKI bespeaks the vulnerability of the kidneys in a state of chronic intrauterine hypoxia.

Within our subgroup of infants with neonatal encephalopathy, we did not find that those with AKI had worse mortality or more ventilator support. When assessing length of stay, we did find that even after controlling for multiple confounders, compared to infants without AKI, those with AKI had an increased adjusted length of stay of 8.5 days. Although there

was a trend towards more oxygen-free and ventilation-free weeks in the group without AKI, small sample size and lack of granularity of this data may have limited our statistical power.

Interestingly, we report for the first time that a lower admission temperature was associated with AKI (Table 1). We speculate possible reasons for this association: first, it is possible that sicker infants (who are more likely to develop AKI) may have been passively or actively cooled at admission, as

**Table 2** Comparison of patient demographics and maternal, perinatal, and postnatal characteristics between infants with AKI with and without neonatal encephalopathy

	AKI; no NE ( <i>n</i> = 364)	AKI ± NE ( <i>n</i> = 47)	<i>p</i> value
Gender (male)	220 (60.4)	23 (48.9%)	0.16
Ethnicity			0.76
Hispanic	31 (10.5%)	3 (8.8%)	
Non-Hispanic	264 (89.5%)	31 (91.2%)	
Race			0.27
White	239 (65.7%)	26 (55.3%)	
Black	49 (13.5%)	10 (21.3%)	
Other	76 (20.9%)	11 (23.4%)	
Gestational age (weeks)			0.047
34–37	113 (31.0%)	8 (17%)	
37 or greater	251 (69.0%)	39 (83.0%)	
Birthweight (g)			0.045
1501–2501	76 (20.9%)	4 (8.7%)	
≥ 2501	283 (77.7%)	42 (91.3%)	
Outborn*	258 (70.9%)	43 (91.5%)	0.002
Mode of delivery			0.97
Cesarean section	144 (42.6%)	18 (42.9%)	
Vaginal birth	194 (57.4%)	24 (57.1%)	
Delivery room resuscitation			
Respiratory support	185 (50.8%)	43 (91.5%)	< 0.0001
Chest compressions	16 (4.4%)	13 (27.7%)	< 0.0001
Epinephrine	10 (2.7%)	9 (19.1%)	< 0.0001
Normal saline bolus	25 (6.9%)	13 (27.7%)	< 0.0001
Admission temp. (°C)	36.6 ± 1.1	34.5 ± 2.2	
Apgar scores			
1 min	8 (4, 8)	1.5 (1.0, 3.0)	< 0.0001
5 min	8 (7, 9)	4.0 (2.0, 6.0)	< 0.0001
Pregnancy characteristics			
Intrapartum infection	37 (10.2%)	5 (10.6%)	0.92
Diabetes	42 (11.5%)	6 (12.8%)	0.80
Gestational hypertension	45 (12.4%)	4 (8.5%)	0.44
IUGR	31 (8.5%)	5 (10.6%)	0.63
Prenatal tobacco use	31 (8.5%)	2 (4.3%)	0.31
Intrapartum complications			
Nuchal cord	31 (8.5%)	12 (25.5%)	0.0003
MSAF	63 (17.3%)	17 (36.2%)	0.002
Severe bleeding	12 (3.3%)	3 (6.4%)	0.29
Shoulder dystocia	6 (1.6%)	3 (6.4%)	0.04
Postpartum factors			
NT drug exposure**	266 (73.1%)	41 (87.2%)	0.03
Fluid overload†	101 (27.7%)	23 (48.9%)	0.003
Bacteremia/meningitis‡	15 (4.1%)	1 (2%)	0.51

Data are *n* (%), mean (SD), median (IQR)

\*Outborn indicates infant born outside the admitting NICU (including home births, birth centers, and lower-acuity facilities)

\*\*NT drug exposure means nephrotoxic drug exposure within first 7 days (gentamicin, vancomycin, furosemide, indomethacin)

† Fluid overload defined as weight > 5% above birth weight at any point in the first 7 days of life

‡ Culture-positive bacteremia or meningitis within the first 7 days of life

AKI acute kidney injury, *g* grams, °C degrees Celsius, *IUGR* intrauterine growth restriction, *MSAF* meconium-stained amniotic fluid

therapeutic hypothermia is standard of care for infants with moderate to severe neonatal encephalopathy [10]. Second, it is possible that neonates that are transported to a referral NICU for hypothermia therapy may in fact be excessively cool at admission [11]. Third, it is possible that outborn status may confound the association between admission temperature and AKI, and finally, it is possible that hypothermia is a marker for severity of illness in term neonates, similar to what has been

seen in premature infants. This data is somewhat contrary to the data reported in a single-center study by Selewski et al. which suggested that the incidence of AKI in NE was lower in the era since hypothermia has become standard of care [12]. The specific impact of hypothermia on AKI in infants with NE needs to be further studied, with careful attention to NE severity and whether or not therapeutic hypothermia was offered.

**Table 3** Multivariate logistic regression to determine associations between risk factors and acute kidney injury

	Odds ratio	95% CI	<i>p</i> value
Outborn	4.28	1.24–14.79	0.02
Intrauterine growth restriction (IUGR)	10.34	1.06–100.47	0.04
Meconium-stained amniotic fluid	2.83	1.04–7.70	0.04

*C* statistic = 0.73. Logistic regression model includes site of delivery, IUGR, exposure to meconium, maternal diabetes, hypertensive gestational diseases (maternal hypertension, pre-eclampsia, or eclampsia) intrapartum nuchal cord complications, nephrotoxic medications, and fluid overload

The aforementioned study by Selewski et al. found a similar incidence of AKI among asphyxiated neonates (38%) between 2003 and 2010 using a relative increase in SCr from baseline to define AKI [12]. This study also found longer length of stay and duration of mechanical ventilation in the AKI group, as well as higher risk of mortality (though not statistically significant.) Our multicenter analysis did not find a mortality difference, likely because death during hospitalization was less common overall. This may be due to the fact that infants with *mild* neonatal encephalopathy are now routinely admitted for therapeutic hypothermia in many centers [13] and comprise a less critically ill patient population. Our study was also unable to demonstrate a difference in the duration or type of respiratory support between infants with and without AKI. This could be due to limitations of the data set with regard to respiratory support beyond the first week of admission, as the AWAKEN database collected continuous data for the first 7 days and then weekly data for each subsequent week of hospitalization [7].

Another single-center prospective study by Alaro et al. in Nairobi examined infants who mostly had mild NE. They defined AKI as a SCr > 133  $\mu\text{mol/L}$  (> 1.5 mg/dL) on day 3 of life [3]. Infants were not offered therapeutic hypothermia. They found a lower prevalence of AKI than in our study (11.7%) likely due to a high threshold value for SCr. Overall mortality in their cohort was nearly 17%. Using this higher

**Table 4** Unadjusted analysis for mortality, and length of stay and respiratory support among infants with neonatal encephalopathy

	No AKI ( <i>n</i> = 66)	AKI ( <i>n</i> = 47)	<i>p</i> value
Mortality	5 (7.6%)	3 (6.4%)	1.00
Length of stay (days)	13.0 ± 9.7	24.2 ± 29.9	0.005
Oxygen-free weeks			0.33
0*	6 (9.1%)	8 (17.0%)	
1–3	20 (30.3%)	16 (34.0%)	
4	40 (60.6%)	23 (48.9%)	
Ventilator-free weeks			0.22
0*	5 (7.6%)	7 (14.9%)	
1–3	8 (12.1%)	9 (19.1%)	
4	53 (80.3%)	31 (66.0%)	

AKI acute kidney injury

\*0 is the reference group

threshold for AKI, the authors found a 24-fold increase in mortality ( $p = 0.001$ ) compared to neonates with NE and no AKI [3]. Our analysis failed to detect a mortality difference; perhaps because we applied a lower threshold to meet the AKI definition, or because this was a broader group of larger and more generalizable group of asphyxiated neonates. Alternatively, the lower mortality in our cohort may have been due to interval improvement in the care of asphyxiated infants, particularly in high-resource tertiary and quaternary centers. It is also possible that our cohort was too small to be powered to detect a mortality difference.

Recent data points to the importance of AKI as a truly independent contributor to morbidity and mortality rather than a marker of illness severity [14]. Studies suggest that therapeutic strategies to mitigate AKI in this population may be warranted, such as the use of single-dose theophylline or aminophylline in patients with NE to prevent AKI [15]. These therapeutic interventions are considered level C [16], and whether this intervention mitigates AKI in the context of therapeutic hypothermia has yet to be determined. Future studies investigating these drugs in context of current clinical practice (therapeutic hypothermia) and evaluating both short- and long-term renal outcomes are necessary.

The strengths of our study include the use of contemporary definitions of AKI including urine output and the multicenter nature of the study. We acknowledge several limitations, primarily those inherent to the retrospective nature of the data collection. The AWAKEN database was designed to capture data related to kidney risk specifically among neonates overall; thus, some variables necessary to characterize a subgroup with NE (e.g., proportion of neonates receiving therapeutic hypothermia, severity of encephalopathy) were not collected. Although our study captured AKI risk in the largest cohort of NE to date, the relatively small sample size limited the precision of our estimates, and we were unable to stratify odds ratios based on AKI severity. While causal inferences cannot be made from observational data, the emergence of IUGR, meconium, low admission temperature, and being outborn as risk factors for AKI merit further exploration.

In conclusion, to our knowledge, this study is the first to report AKI incidence and explore risk factors and outcomes in a multi-national cohort of infants with NE. This study confirms that AKI occurs frequently in neonatal encephalopathy

**Table 5** Adjusted prediction model for length of stay

	Crude Parameter estimate*	<i>p</i> value	Adjusted Parameter estimate*	<i>p</i> value
Length of stay (days)	11.05 (3.27–18.83)	0.01	8.48 (0.79–16.2)	0.03

\*Linear model for length of stay adjusted for intrauterine growth restriction, maternal diabetes, hypertensive gestational diseases, nuchal cord complications, nephrotoxic medications, and fluid overload

and is associated specifically with being outborn, IUGR, or having MSAF (a marker of antenatal stress), and low admission temperature. Infants with AKI have longer length of stay, even after adjusting for confounders. Survivors of NE merit inpatient monitoring for AKI and specific protocols for its management, as well as blood pressure screening by primary care pediatricians after discharge as recommended by the American Academy of Pediatrics [17]. Future prospective research should be directed at improving diagnosis of AKI in the early neonatal period using biomarkers that account for unique neonatal physiology and characterizing long-term renal outcomes in survivors of neonatal encephalopathy.

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## Compliance with ethical standards

Institutional Review Board (IRB) approval was obtained at each participating site with a waiver of informed consent.

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