Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study

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Summary

Background **Findings from single-centre studies suggest that neonatal acute kidney injury (AKI) is associated with poor outcomes. However, because of the small sample size of those studies, few inferences can been made regarding the independent associations between AKI, mortality, and hospital length of stay. We aimed to establish whether neonatal AKI is independently associated with increased mortality and length of hospital stay.**

Methods **We did this multicentre, multinational, retrospective cohort study of critically ill neonates admitted to 24 participating neonatal intensive care units (NICUs) in four countries (Australia, Canada, India, USA) between Jan 1 and March 31, 2014. We included infants born or admitted to a level 2 or 3 NICU and those who received intravenous fluids for at least 48 h. Exclusion criteria were admission at age 14 days or older, congenital heart disease requiring surgical repair within 7 days of life, lethal chromosomal anomaly, death within 48 h of admission, inability to determine AKI status, or severe congenital kidney abnormalities. We defined AKI as an increase in serum creatinine of 0·3 mg/dL or more (≥26·5 μmol/L) or 50% or more from the previous lowest value, or a urinary output of less than 1 mL/kg per h on postnatal days 2–7. We used logistic regression to calculate crude odds ratios (ORs) and associated 95% CIs for the association between AKI and likelihood of death. We used linear regression to calculate the crude parameter estimates and associated 95% CIs for the association between AKI and length of hospital stay. Multivariable logistic and linear regression models were run to account for potential confounding variables. We additionally created regression models stratified by gestational age groups (22 weeks to <29 weeks, 29 weeks to <36 weeks, and ≥36 weeks). This study is registered with ClinicalTrials.gov, number NCT02443389.**

Findings **We enrolled 2162 infants, of whom 2022 (94%) had data to ascertain AKI status. 605 (30%) infants had AKI. Incidence of AKI varied by gestational age group, occurring in 131 (48%) of 273 of patients born at 22 weeks to less than 29 weeks, 168 (18%) of 916 patients born at 29 weeks to less than 36 weeks, and 306 (37%) of 833 patients born at 36 weeks or older. Infants with AKI had higher mortality than those without AKI (59 [10%] of 605 *vs* 20 [1%] of 1417 infants; p<0·0001), and longer length of hospital stay (median 23 days [IQR 10–61] *vs* 19 days [9–36]; p<0·0001). These findings were confirmed in both crude analysis of mortality (OR 7·5, 95% CI 4·5–12·7; p<0·0001 for AKI *vs* no AKI) and length of stay (parameter estimate 14·9 days, 95% CI 11·6–18·1; p<0·0001) and analysis adjusted for multiple confounding factors (adjusted OR 4·6, 95% CI 2·5–8·3; p<0·0001 and adjusted parameter estimate 8·8 days, 95% CI 6·1–11·5; p<0·0001, respectively).**

Interpretation **Neonatal AKI is a common and independent risk factor for mortality and increased length of hospital stay. These data suggest that AKI might have a similar effect in neonates as in paediatric and adult patients. Strategies designed to prevent AKI and treatments to reduce the burden of AKI, including renal support devices designed for neonates, are greatly needed to improve the outcomes of these vulnerable infants.**

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Introduction

Study of acute kidney injury (AKI) in critically ill neonates has lagged behind that in older populations; however, the past 5 years have seen an intensification of research in this area. Findings from small, single-centre studies in neonates with congenital heart disease,[1–3] sepsis,[4–6] and hypoxic ischaemic injury;[6–8] infants who receive extracorporeal membrane oxygenation;[9,10] and infants of very low birthweight[11–15] suggest that AKI is common and that neonates and children with AKI have worse outcomes than do those without the disorder.

Although provocative, multicentre studies that use a contemporary definition and incorporate large sample sizes are needed to enable adjustment for multiple potential confounders and allow for generalisability. Moreover, studies that encompass the entire neonatal intensive care unit (NICU) population might offer comparative insights across different gestational age groups.

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Research in context

Evidence before this study

We searched PubMed between Jan 1, 2006, and Dec 31, 2016, for studies of acute kidney injury (AKI) in neonates, with the search terms "neonatal", "neonate", "infant", "kidney injury", "acute kidney injury", "renal failure", "acute renal failure". We reviewed the reference lists of each study obtained through PubMed to identify additional studies not previously detected. The multidisciplinary nature of the Neonatal Kidney Collaborative allowed for input from members familiar with both the neonatology and the paediatric nephrology literature. Studies identified included either retrospective or prospective observational data from single centres with small sample sizes. Most studies were limited to specific subsets of patients, such as very low birthweight infants, infants with perinatal asphyxia or sepsis, or infants receiving extracorporeal membrane oxygenation. Only one study included urinary output criteria in the definition of AKI; the rest used only serum creatinine-based definitions. Multiple different serum creatinine-based AKI definitions have been used, making data comparison across studies difficult. The incidence of neonatal AKI based on published studies ranges from 3% to 71%—a wide range that reflects heterogeneity in patient selection, frequency and type of monitoring, and the AKI definition used. Most studies show that AKI is associated with poor outcomes, but are limited by small sample size when controlling for potential confounders.

Added value of this study

To our knowledge, the Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN) study is the largest neonatal AKI study to date. It is the first multicentre, multinational project and the first to include infants admitted to the neonatal intensive care unit (NICU) across the gestational age spectrum, allowing us to make comparisons across gestational age groups. Our findings show that about 30% of sick neonates admitted to the NICU develop AKI, and that neonatal AKI is associated with morbidity and mortality independent of multiple potential confounders. Use of a standardised AKI definition modified from one that is widely accepted for use in paediatric and adult cohorts allows for comparison of our data to those from adult and paediatric intensive care unit populations. This study will help move the field forward toward the establishment of a common framework for neonatal AKI research.

Implications of all the available evidence

This work improves our understanding of the incidence of AKI in the NICU and its association with important clinical outcomes in these patients. AKI affects neonates of all gestational ages. Consistent with studies in other critically ill populations, neonatal AKI is not simply an incidental finding, but a key event that affects mortality and hospital length of stay. Future studies that capture AKI systematically during high-risk events are greatly needed. With AWAKEN as a foundation, additional studies will provide data needed to support the development of evidence-based monitoring guidelines for use by neonatologists, paediatricians, and paediatric nephrologists as they care for patients with AKI in the NICU and those at risk for chronic kidney disease in the future. Strategies designed to prevent AKI and treatments to reduce the burden of AKI, including renal support devices designed for neonates, are greatly needed to improve the outcomes of these vulnerable infants.

We did the Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN) study to establish whether neonatal AKI is independently associated with increased mortality and length of hospital stay. We hypothesised that neonatal AKI would be associated with increased mortality and length of stay in the NICU, independent of demographics, comorbidities, and severity of illness.

Methods

Study design and participants

We did this multicentre, multinational, retrospective cohort study of critically ill neonates from 24 centres participating in the Neonatal Kidney Collaborative (NKC)[16] in Australia, Canada, India, and the USA. A complete description of the formation of the NKC and methods for development of the AWAKEN database have been published elsewhere.[16]

We reviewed medical records for all neonates admitted to level 2–4 NICUs between Jan 1 and March 31, 2014. We included neonates admitted within the study period and those who received intravenous fluids for at least 48 h. Exclusion criteria were admission at age 14 days or older, congenital heart disease requiring surgical repair within 7 days of life, lethal chromosomal anomaly, death within 48 h of NICU admission, and severe congenital kidney and urinary tract abnormalities. We selected these criteria to enable enrolment of infants who were most likely to have measurements for serial serum creatinine and urinary output. Babies admitted to the NICU without need for intravenous fluids are generally only mildly ill (ie, transient tachypnoea of the newborn, transient hypoglycaemia, advancement of feeds) and receive intensive care for only a short period.

The institutional review board (IRB) of the University of Alabama at Birmingham approved this collaborative study, and each centre received approval from their respective IRBs. The study design allowed for a waiver of informed consent or parental permission.

Data collection

The variables extracted were chosen based on their relevance to the study of neonatal AKI. All data, including frequency of laboratory monitoring, reflect local standards of care and were dictated by the treating

clinicians. All data were entered and stored in MediData RAVE (version 2014.2.0)—a web-based database.

Detailed description of data collection for AWAKEN has been previously published.[16] Briefly, we organised data into five components: baseline demographics, daily information for week 1, weekly snapshots for the remainder of the time in hospital, discharge data (captured at discharge or 120 days of age, whichever came first), and prolonged length-of-stay data for infants who were in hospital for longer than 120 days.

Definition of acute kidney injury

All serum creatinine values obtained during the study period were recorded. We defined AKI as an increase in serum creatinine of 0·3 mg/dL or more (≥26·5 µmol/L) or 50% or more from the previous lowest value, or a urinary output of less than 1 mL/kg per h on postnatal days 2–7, according to the Kidney Disease: Improving Global Outcomes (KDIGO) workgroup AKI definition[17] modifed for neonates, as used in previous neonatal studies[18–21] (appendix). This definiton differs from KDIGO in three ways. First, urinary output is reported in 24 h increments rather than in 6–12 h blocks, because most centres did not record urinary output on an hourly basis. Second, to classify a patient with serum creatinine-defined AKI, each measurement was compared with the lowest previous measurement to detect both an absolute and a percentage rise from baseline. Comparison with the lowest previous serum creatinine value is necessary because serum creatinine values normally decline over the first weeks after birth, such that the baseline value is constantly changing. Third, a serum creatinine cutoff of 2·5 mg/dL (221 µmol/L), rather than 4·0 mg/dL (353·6 µmol/L) as used in adults, was used for stage 3, since the cutoff of 2·5 mg/dL yields a glomerular filtration rate of less than 10 mL/min per 1·73 m².

When an infant had less than two serum creatinine measurements assessed during hospital admission, we deemed data insufficient for classification of serum creatinine-defined AKI. The urinary output threshold for AKI was set at 1 mL/kg per h or less averaged over 24 h on days 2–7 after birth. If an infant did not have at least 1 day with quantifiable urinary output in the medical record, we deemed data insufficient for classification of urinary output-defined AKI. Either diaper or catheter urine collection was acceptable as long as the urinary output was quantifiable. Infants were classified as having AKI if they met either the serum creatinine or urinary output definitions. The maximum AKI stage was classified as the highest of either serum creatinine or urinary output criteria. AKI severity was classified into one of three stages by use of traditional KDIGO methods (appendix).

Severity of illness score

We used the clinic risk index for babies II (CRIB II) score[22] to assess severity of illness for infants in the 22 weeks or older to younger than 29 week cohort for gestational age. This risk adjustment tool for assessing the probability of mortality incorporates five variables: sex, birthweight, gestational age, temperature at admission (°C), and base excess (mmol/L). This scoring system was validated in infants with a gestational age of 32 weeks or younger; therefore, it was incorporated only into the models for the youngest gestational age cohort. No available, validated severity of illness scores are available for infants with a gestational age of 32 weeks or more.

Statistical analysis

Categorical variables were analysed by proportional differences with either χ^2 or Fisher's exact tests. All continuous variables were tested for normality with the Shapiro–Wilk test. For normally distributed continuous variables, we determined means and SDs with the Student's *t* test. For non-normally distributed variables, we determined medians and IQRs, and compared groups with the Wilcoxon signed-ranks test. We used logistic regression to calculate crude odds ratios (ORs) and associated 95% CIs for the association between AKI and likelihood of death. We used linear regression to calculate crude parameter estimates and associated 95% CIs for the association between AKI and length of stay. Multivariable logistic and linear regression models were run to account

See Online for appendix

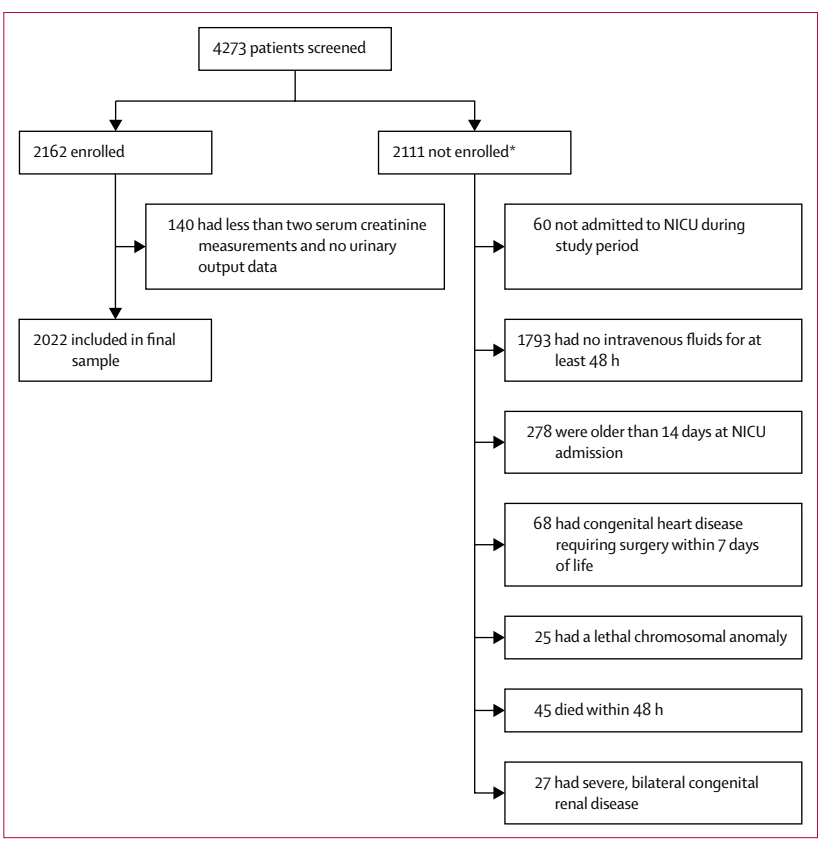

***Figure 1*: Study flow chart**
NICU=neonatal intensive care unit. *Some patients were excluded for more than one reason.

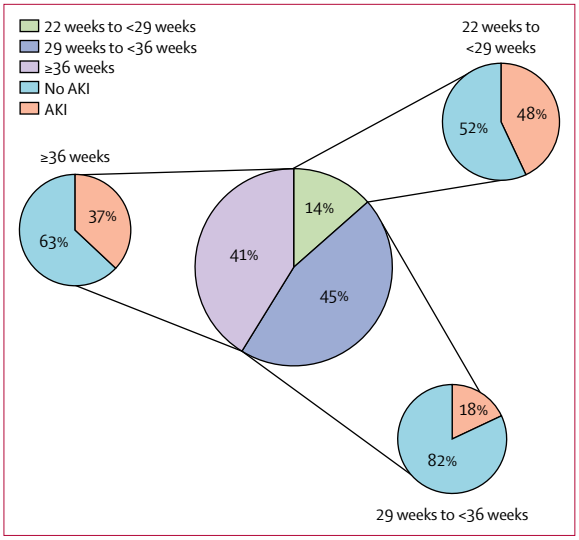

Figure 2: **Gestational age distribution and AKI incidence**
AKI=acute kidney injury.

		Serum creatinine AKI status			
		Missing	No	Yes	Total
Urinary output AKI status	Missing	140 (7%)*	177 (9%)	66 (3%)	243 (12%)
	No	469 (22%)	771 (38%)	258 (13%)	1498 (74%)
	Yes	92 (4%)	133 (7%)	56 (3%)	281 (14%)
	Total	561 (28%)	1081 (53%)	380 (19%)	2022 (100%)

Figure 3: **AKI (any stage) by urinary output and serum creatinine criteria (N=2022)**
Data are n (%). AKI=acute kidney injury. *Excluded from all calculations because of insufficient data for both urinary output and serum creatinine.

for potential confounding variables, and findings are reported as adjusted OR and adjusted parameter estimate, respectively. Adjusted regression models were constructed with a backwards selection procedure with a significance level to stay of less than 0·2. Separate regression models were created for the whole cohort and cohorts stratified by gestational age groups (22 weeks to <29 weeks, 29 weeks to <36 weeks, and ≥36 weeks).

We did time-to-event analysis for survival by AKI status and maximum AKI stage with Kaplan–Meier analysis of the entire cohort and for each gestational age category. A p value of less than 0·05 was considered statistically significant.

The design of this study did not allow for standardised assessment of serum creatinine or urinary output values. We did a post-hoc sensitivity analysis of infants in whom AKI status could not be determined. To determine whether these missing data would have affected our results significantly, we did best-case and worst-case sensitivity analyses for the incidence of AKI, hospital survival, and hospital length of stay. Similarly, we did a post-hoc sensitivity analysis to determine differences between infants born at centres that measured serum creatinine more often (median five or more counts per infant) versus less often (less than five counts).

We did analyses with SAS (version 9.4). This study is registered with ClinicalTrials.gov, number NCT02443389.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. DA, LJB, and RLG had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results

We enrolled 2162 infants, of whom 2022 (94%) had data to ascertain AKI status and comprised the final sample (figure 1). Within the cohort stratified by gestational age group, 273 (14%) patients were 22 weeks to younger than 29 weeks old, 916 (45%) were 29 weeks to younger than 36 weeks, and 833 (41%) were 36 weeks or older (figure 2).

561 (28%) patients had fewer than two serum creatinine measurements and 243 (12%) patients had no quantifiable urinary output data for the first week of life (figure 3). Of these patients, 140 (7%) neonates had both fewer than two serum creatinine values and insufficient urinary output data, and therefore could not be given any AKI classification and were excluded from the analysis (figure 3). Of the remaining sample, 281 (14%) of 2022 patients had urinary output-defined AKI and 380 (19%) patients had serum creatinine-defined AKI (figure 3). Only 56 (3%) infants had AKI defined by both measurements (figure 3). 605 (30%) patients had AKI defined by either serum creatinine or urinary output criteria. When classified according to highest AKI stage, 281 (14%) patients reached stage 1, 143 (7%) reached stage 2, and 181 (9%) reached stage 3 (appendix). AKI varied substantially between gestational age groups (figure 2).

Overall, 56% of infants were boys, most were white, and 18% were neonates of multiple gestation (table 1). The most common reasons for NICU admission were prematurity less than 35 weeks, respiratory failure, and sepsis evaluation (table 1). Roughly three-quarters of infants were discharged home before 120 days of age; 4% either died in hospital or were in hospital for 120 days or more (table 1).

Compared with infants without AKI, those with AKI were more likely to belong to the highest birthweight category, to have been born outside the participating hospitals (ie, outborn), and to be admitted for hypoxic ischaemic encephalopathy, seizures, congenital heart disease, necrotising enterocolitis, and surgical evaluation; they were less likely to be admitted for prematurity or sepsis assessment (table 1). Polyhydramnios was more frequent in the AKI group than in the group with no AKI (table 1). There was no difference between groups in rates

	No AKI (n=1417)	AKI (n=605)	p value
Infant variables			
Sex	..	..	0·12
Female	622 (44%)	258 (43%)	..
Male	795 (56%)	347 (57%)	..
Ethnic origin	..	..	0·03
Hispanic	198 (14%)	60 (10%)	..
Non-Hispanic	1004 (71%)	441 (73%)	..
Unknown	215 (15%)	104 (17%)	..
Race	..	..	0·07
White	777 (55%)	364 (60%)	..
Black	271 (19%)	107 (18%)	..
Other	369 (26%)	134 (22%)	..
Site of delivery (outborn)	505 (36%)	349 (58%)	<0·0001
Gestational age	..	..	<0·0001
22 weeks to <29 weeks	142 (10%)	131 (22%)	..
29 weeks to <36 week	748 (53%)	168 (28%)	..
≥36 weeks	527 (37%)	306 (51%)	..
Birthweight (g)	..	..	<0·0001
≤1000	112 (8%)	119 (20%)	..
1001–1500	238 (17%)	57 (9%)	..
1501–2500	552 (39%)	124 (21%)	..
≥2501	513 (36%)	302 (50%)	..
Apgar score	..	..	..
1 min	7·00 (5·00–8·00)	6·00 (3·00–8·00)	<0·0001
5 min	8·00 (7·00–9·00)	8·00 (6·00–9·00)	<0·0001
Reason for admission*	..	..	
Prematurity <35 weeks	791 (56%)	263 (43%)	<0·0001
Respiratory symptoms	314 (22%)	150 (25%)	0·20
Respiratory failure	651 (46%)	281 (46%)	0·84
Sepsis evaluation	742 (52%)	274 (45%)	0·004
Hypoxic ischaemic encephalopathy	70 (5%)	48 (8%)	0·01
Seizures	33 (2%)	37 (6%)	<0·0001
Hypoglycaemia	168 (12%)	50 (8%)	0·02
Hyperbilirubinaemia	32 (2%)	29 (5%)	0·002
Metabolic evaluation	8 (1%)	12 (2%)	0·003
Trisomy 21	14 (1%)	9 (1%)	0·33
Congenital heart disease	34 (2%)	48 (8%)	<0·0001
Necrotising enterocolitis	6 (<1%)	15 (2%)	<0·0001
Omphalocele and gastroschisis	32 (2%)	15 (2%)	0·76
Need for surgical evaluation	47 (3%)	48 (8%)	<0·0001
Meningomyelocele	9 (1%)	8 (1%)	0·12
Small for gestational age	306 (22%)	117 (19%)	0·27
Large for gestational age	58 (4%)	40 (7%)	0·02
(Continued from previous column)			
Maternal variables			
Age (years)	28·6 (6·2)	28·3 (5·9)	0·24
Infections	..	..	..
Bacterial	120 (8%)	66 (11%)	0·08
Viral	35 (2%)	23 (4%)	0·10
Diabetes	203 (14%)	68 (11%)	0·06
Hypothyroidism	64 (5%)	33 (5%)	0·37
Chronic hypertension	140 (10%)	38 (6%)	0·01
Kidney disease	12 (1%)	6 (1%)	0·75
Pre-eclampsia	220 (16%)	67 (11%)	0·01
Eclampsia	17 (1%)	8 (1%)	0·82
Intrauterine growth retardation	136 (10%)	52 (9%)	0·48
Oligohydramnios	65 (5%)	33 (5%)	0·41
Polyhydramnios	39 (3%)	34 (6%)	0·002
Haemorrhage	40 (3%)	23 (4%)	0·25
Multiple gestation	291 (21%)	67 (11%)	<0·0001
Assisted conception	112 (8%)	37 (6%)	0·003
Drugs used during pregnancy	..	..	..
Steroids	563 (40%)	173 (29%)	<0·0001
ACE inhibitors	0	0	NA
NSAIDs	46 (3%)	16 (3%)	0·47
Antihypertensives	172 (12%)	44 (7%)	0·002
Illicit drugs	115 (8%)	49 (8%)	0·99
Tobacco	156 (11%)	64 (11%)	0·78
Alcohol	27 (2%)	9 (1%)	0·52
SSRIs	42 (3%)	17 (3%)	0·85
Intrapartum complications	..	..	..
Nuchal cord	85 (6%)	40 (7%)	0·60
Meconium	142 (10%)	74 (12%)	0·14
Severe vaginal bleeding	58 (4%)	33 (5%)	0·18
Shoulder dystocia	13 (1%)	7 (1%)	0·62
Disposition	..	..	<0·0001
Discharged within 120 days	1156 (82%)	400 (66%)	..
Still in NICU at ≥120 days	28 (2%)	53 (9%)	..
Transfer convalescent care	200 (14%)	73 (12%)	..
Transfer escalated care	13 (1%)	20 (3%)	..
Died in hospital	20 (1%)	59 (10%)	..

Data are n (%), median (IQR), or n (%), unless otherwise specified. AKI=acute kidney injury. ACE=angiotensin-converting enzyme. NSAID=non-steroidal anti-inflammatory drug. SSRI=selective serotonin uptake inhibitors. NA=not applicable. NICU=neonatal intensive care unit. *Patients could have had more than one reason for admission.

***Table 1*: Patients' characteristics**

of oligohydramnios and intrauterine growth restriction, or in infants' sex (table 1). Mothers of infants with AKI were less likely to have chronic hypertension or pre-eclampsia, or to have received steroids or antihypertensives (table 1).

	Any AKI			Maximum AKI stage				
	No (n=1417)	Yes (n=605)	p value	0 (n=1417)	1 (n=281)	2 (n=143)	3 (n=181)	p value
Survived	..	..	<0·0001	..	..	..	..	<0·0001
Yes	1397 (99%)	546 (90%)	..	1397 (99%)	255 (91%)	133 (93%)	158 (87%)	
No	20 (1%)	59 (10%)	..	20 (1%)	26 (9%)	10 (7%)	23 (13%)	
Length of stay (days)	19 (9–36)	23 (10–61)	<0·0001	19 (9–36)	18 (9–55)	30 (11–79)	27 (13–59)	<0·0001

Data are n (%) or median (IQR). 140 enrolled patients had less than two serum creatinine measurements and no urinary output data. Among patients who did not die, 306 were transferred for convalescence or escalation of care. AKI=acute kidney injury.

***Table 2*: Clinical outcomes by AKI status**

	Crude odds ratio or parameter estimate (95% CI)	p value	Adjusted odds ratio or parameter estimate (95% CI)	p value
Mortality	7·5 (4·5–12·7)	<0·0001	4·6 (2·5–8·3)*	<0·0001
Length of stay (days)	14·9 (11·6–18·1)	<0·0001	8·8 (6·1–11·5)†	<0·0001

Crude odds ratios are presented for mortality and parameter estimates for length of stay. *Logistic model for mortality adjusted for neonatal height, admission for seizures, admission for congenital heart disease, mode of delivery, neonatal intubation, neonatal chest compression, and admission for other reasons. †Linear model for length of stay adjusted for gestational age, birthweight, neonatal intubation, neonatal chest compression, admission for prematurity, admission for respiratory symptoms, admission for respiratory failure, admission for necrotising enterocolitis, admission for omphalocele, maternal multiple gestation, maternal use of non-steroidal anti-inflammatory drugs, neonatal height, neonatal head circumference, neonatal Apgar score at 5 min, and admission for other reasons.

***Table 3*: Prediction models for clinical outcomes**

Maternal history of eclampsia, kidney disease, illicit drug exposure, and intrapartum complications did not differ significantly between groups (table 1).

Clinical care of critically ill neonates, and frequency of monitoring of kidney function, reflect local standards of care. The appendix provides a summary of serum creatinine counts, rates of AKI, country, type of serum creatinine assay, and mortality outcomes by centre. Median serum creatinine counts per patient varied from one (IQR one to one) to 11 (three to 26). Incidence of AKI by centre varied from 3% to 74%, with higher AKI rates noted in the centres with more serum creatinine counts per patients. Survival rates varied from 78% to 100%, with only one US centre reporting a rate of less than 90%.

First AKI events occurred most often during the first week after birth for the entire cohort and for the two older gestational age groups (appendix). Infants with a gestational age of 22 weeks to younger than 29 weeks had proportionally more AKI events after the first week than did those in the two older age groups (appendix).

Mortality was higher in infants with serum creatinine-defined or urinary output-defined AKI than in those without AKI (table 2). Infants with stage 3 AKI had higher mortality rates than did those with stage 2 or stage 1 AKI (table 2). Infants with AKI also had longer hospital length of stay than those without AKI (table 2). Length of stay was longer in infants with higher stages of AKI (stages 2 and 3) than in those with no AKI (table 2).

AKI was significantly associated with increased mortality and hospital length of stay in both crude analysis and analysis adjusted for multiple demographic characteristics, interventions, and comorbidities (table 3). Survivors with AKI had longer length of stay than did those without AKI (median 23 days [IQR 11–64] *vs* 19 days [9–36]; p<0·0001). Length of stay did not differ significantly between non-survivors with AKI and non-survivors without AKI (median 13 days [IQR 5–21] *vs* 15 [5–33]; p=0·38).

The appendix shows outcomes stratified by gestational age group. Evaluation of the gestational age groups showed that, after controlling for potential confounders, AKI status was independently associated with increased odds of death for the group born at 22 weeks to less than 29 weeks (adjusted OR 3·7, 95% CI 1·4–9·7), the group born at 29 weeks to less than 36 weeks (5·1, 1·6–16·5), and the group born at 36 weeks or older (3·9, 1·2–13·2; appendix). However, an association between AKI and length of stay was shown only in the two oldest gestational groups (29 weeks to <36 weeks: β parameter estimate 9·6, 95% CI 5·4–13·8; ≥36 weeks: 11·0, 8·0–14·0), but not in the youngest age group (0·5, –11·1 to 12·1; appendix).

Mortality in the 140 infants who could not be given an AKI classification because of insufficient data for serum creatinine or urinary output was similar to that in infants in the group with no AKI (four [3%] of 140 *vs* 20 [1%] of 1417 infants; p=0·18).

Most infants died within the first 50 days of hospital admission (figure 4). Survival was worse in infants with AKI than in those without AKI (figure 4). When stratified according to AKI stage, infants with stage 3 AKI had worse survival outcomes than did those with stage 2 or stage 1 disorder, or those with no AKI (figure 4). Notably, infants in the stage 1 group had worse survival than did those in the stage 2 group (p<0·0001; figure 4). Findings were similar when the survival curves were stratified by gestational age category (appendix).

In sensitivity analysis of the worst-case scenario (n=140 with missing data had AKI), 745 (34%) of 2162 infants had AKI. AKI was significantly associated with mortality (crude OR 6·4, 95% CI 3·9–10·7; p<0·0001) and hospital length of stay (crude parameter estimate 8·7 days, 95% CI 5·7–11·6; p<0·0001). After adjustment, infants with AKI had higher odds of death (adjusted OR 4·2,

95% CI 2·3–7·6; p<0·0001) and longer hospital length of stay (adjusted parameter estimate 5·3 days, 95% CI 2·9–7·8; p<0·0001) than did those with no AKI. In the best-case scenario (n=140 with missing data did not have AKI), 605 (28%) of 2162 infants did have AKI. AKI was significantly associated with mortality (crude OR 6·9, 95% CI 4·2–11·2; p<0·0001) and hospital length of stay (crude parameter estimate 16·5 days, 95% CI 13·4–19·6; p<0·0001). After adjustment, infants with AKI had higher odds of death (adjusted OR 3·6, 95% CI 2·0–6·2; p<0·0001) and longer hospital length of stay (adjusted parameter estimate 9·6 days, 95% CI 7·0–12·2; p<0·0001) than did those with AKI. This finding suggests that these patients with missing classification did not affect the overall findings.

As expected, incidence of AKI in the centres that measured serum creatinine often (median five or more counts per infant) was higher than the incidence of AKI in centres that measured serum creatinine less often (less than five counts per infant; 347 [41%] of 840 *vs* 258 [22%] of 182 infants; p<0·0001). Regardless of whether infants were in centres that checked serum creatinine often or not, infants with AKI had higher adjusted odds of death and length of stay than did infants without AKI. Specifically, in centres that did checks often, the adjusted OR for death was 3·1 (95% 1·3–7·4; p=0·01), and for length of stay was 13 (8·2–17·7; p<0·0001); in centres that did checks less often, the adjusted ORs were 6·1 (2·5–14·6; p<0·0001) and 4·4 (1·2–7·7; p=0·01), respectively.

Renal replacement therapy (RRT) was done in 25 (4%) of 605 neonates with AKI, which accounts for 25 (1%) of 2022 neonates enrolled in the study and 25 (1%) of 4273 neonates admitted to the NICU during the 3 month period. Types of RRT included peritoneal dialysis alone (n=9), continuous RRT (n=4), continuous RRT plus extracorporeal membrane oxygenation (n=11), and peritoneal dialysis plus continuous RRT (n=1). No infants were dialysed with intermittent haemodialysis or sustained low-efficiency dialysis. Of infants who received RRT, 19 (76%) survived. Infants with AKI who had RRT had lower survival than those with AKI who did not have RRT (19 [76%] *vs* 527 [91%] of 580; p=0·01). Hospital length of stay was numerically, albeit not significantly, longer in infants with AKI who did not have RRT than in those who did have RRT (median 43 days [IQR 22–103] *vs* 22 days [10–61]; p=0·07).

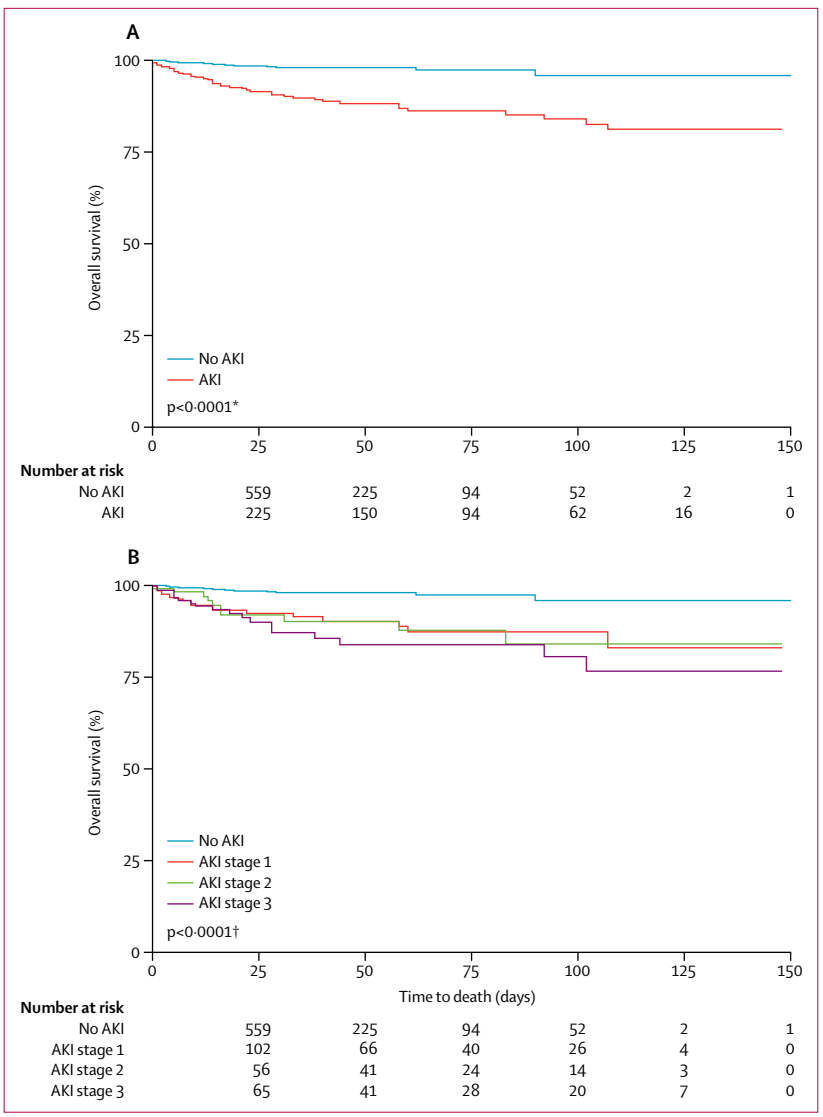

***Figure 4*: Survival outcomes**
Survival curves for the entire cohort by any AKI (A) and and by stages of AKI (B). AKI=acute kidney injury. *Survival was worse in infants with AKI than in those without AKI. †Survival was worse in infants with stage 3 AKI than in those with stage 2, 1, or no AKI.

Discussion

The overall incidence of AKI in neonates enrolled in the AWAKEN study was 30%, and infants with AKI had four-times higher independent odds of death and longer independent hospital length of stay than those without AKI. These data support findings from studies of other critically ill neonates,[1–15] children,[23] and adults,[24] which show that AKI is associated with poor outcomes, even after controlling for numerous confounders. The large sample size highlights practice variations in monitoring for neonatal AKI and shows differences in AKI incidence and outcomes across gestational age categories.

Although the overall incidence of AKI was 30%, the incidence by gesational age category showed a U-shaped distribution, with the highest rates in the oldest (>36 weeks) and youngest (22 weeks to <29 weeks) neonates. The incidence of AKI in the youngest gestational age group was 48%—a finding in line with published single-centre studies.[10–15] Similarly, the AKI rate in infants born at 36 weeks or older (37%) is consistent with those in other studies of term infants.[6–8] AKI incidence in the group born at 29 weeks to younger than 36 weeks (18%) has not been reported previously. Our data suggest that infants in this middle group are

also at risk for AKI, but not to the same extent as at-risk neonates of other ages. One possible explanation might be that these infants are not as critically ill as the lowest age and full-term gestational age groups. Compared with infants in the middle gestational age group, those in the lowest age group were more often outborn, had lower 1 min and 5 min Apgar scores, and had higher rates of respiratory failure, sepsis evaluation, hypoxic ischaemic encephalopathy, necrotising enterocolitis, and maternal vaginal bleeding. Infants in the lowest age category were less likely to be born small for gestational age and less likely to be born to mothers with pre-eclampsia. Infants delivered because of medical maternal conditions, such as pre-eclampsia, tend to be less ill than infants born premature for other reasons (ie, chorioamnionitis). Compared with the middle gestational age group, infants in the full-term group were more likely to be outborn, had higher rates of hypoxic ischaemic encephalopathy, were more often born to mothers with maternal infection, and more likely to be born with meconium-stained fluid.

We used the KDIGO definition adapted for neonates for several reasons. First, an AKI workshop explored this definition and concluded that, although adjustments to the definition might be needed in the future as more data become available, this definition was a reasonable starting point for accrual of epidemiology data on neonatal AKI.[25] Second, because this definition is the most widely accepted definition of AKI in paediatric and adult cohorts, it allowed us to compare our data with other populations. Indeed, the AKI rates we documented in NICU patients are similar to those shown in multicentre studies of paediatric and adult ICU groups. For example, findings from the AWARE study, a multinational cohort of critically ill paediatric patients, showed an AKI incidence of 26%.[23] Similarly, AKI-EPI, an adult multicentre study published in 2015,[24] showed an AKI incidence of 57%. AWAKEN, AWARE, and AKI-EPI all show that AKI is independently associated with clinical outcomes in ICU patients, higher stages of AKI portend worse outcomes, and inclusion of urinary output in the definition of AKI identifies patients with renal injury who would not have been detected by changes in serum creatinine alone. As in the AWARE study, we found that most infants with serum creatinine-defined AKI did not have urinary output-defined AKI, and vice versa. Despite these similarities, AWAKEN differs from AWARE on the basis of differences in the study populations: AWARE excluded children younger than 3 months, and the comorbid conditions, stage of glomerular development, and baseline kidney function differ between neonates and children older than 3 months. Nevertheless the conclusions remain similar: AKI is common and is independently associated with clinically significant outcomes. Thus, patients do not just die with AKI, rather, AKI is likely to be a crucial component in the disease process.

Few infants met criteria for both types of AKI, which could be because of poor tubular function in premature infants; high rates of nephrotoxic medications, which are known to cause non-oliguric AKI; or possibly because of ascertainment bias, since we only captured urinary output data during the first week of life. If urinary output was not measured, the incidence of AKI would have been reduced by about a third. Our findings suggest that quantification of urinary output is an important part of assessment for neonatal AKI. Given the difficulty in placement of urinary catheters in some infants, and efforts to minimise catheter-associated urinary tract infections in many institutions, weighing of diapers might be a necessary and reasonable method (although perhaps not completely accurate, especially when urine is mixed with stool). To date, only a few studies have rigorously assessed oliguria as a measure of neonatal AKI.[2,26] Because of the retrospective study design, we used cutoff values for urinary output with 24 h increments. A prospective study that documents urinary output hourly and accounts for factors that could affect urinary output (eg, use of diuretics) is greatly needed to delineate the most clinically significant threshold for oliguria in infants.

Kidney function surveillance patterns and AKI rates differed substantially across centres. The site with the lowest AKI rate also had the lowest number of serum creatinine checks, whereas the site with the highest rate checked serum creatinine much more often. These findings suggest that incidence of neonatal AKI would have been even higher if more rigorous AKI surveillance protocols were implemented. Indeed, evidence-based guidelines that outline optimal methods for monitoring kidney function in neonates are greatly needed.

The frequency of RRT use in NICUs has not been previously described. Our data show that RRT is used very sparingly in NICUs. Despite the little use, rates of survival in these cohorts are better than those reported in a large paediatric continuous RRT registry, which showed that survival in children weighing less than 5 kg was 44%.[27] Not surprisingly, infants who received RRT had higher mortality than infants in the entire cohort and those with AKI who did not receive RRT. This finding is likely to be due to the increased severity of illness and comorbidities in infants who receive RRT. We presume that without RRT, the survival in patients who received RRT would have been much worse. Having RRT devices available that were specifically designed for neonates could have increased the use of these devices in neonates with AKI, and presumably provided a better chance for survival. The high incidence and mortality ascribed to AKI in NICU is justification for exploration of preventive and therapeutic strategies to minimise the effects of AKI, and implementation of safer RRT devices designed specifically for neonates.[28]

The strengths of our study include the large neonatal cohort, multicentre approach, and successful collaboration between neonatology, paediatric nephrology, and epidemiology experts in neonatal AKI. These factors

enabled a robust analysis that adjusted for potential confounders and included prespecified contemporary definitions. Multidisciplinary collaboration improves the accuracy in interpretation of clinical data and events.

Despite these strengths, we acknowledge several important limitations. First, because this is a retrospective study, we had to rely on serum creatinine and urinary output data available in the medical records; therefore, AKI cases could have been missed. We tried to mitigate this issue by excluding patients with insufficient serum creatinine and urinary output data from outcomes analyses, and did best-case and worst-case sensitivity analyses, which showed that the absence of data for 140 patients in whom AKI status could not be determined did not change our results substantially—ie, the associations with mortality and length of stay remained significant in both scenarios. Second, although the neonatal AKI definition used for this study has been vetted by an expert panel, the definition continues to be empirical. Our findings support use of this definition in the future, although refinement might be necessary. Two groups for which use of this definition requires additional clarification are infants whose serum creatinine does not decline in the first week of life, and infants born with a very high concentrations of serum creatinine due to maternal kidney disease. Future prospective studies should explore how different cutoffs for serum creatinine and urinary output, and incorporation of other urinary and serum biomarkers, could improve the ability to reliably define AKI. Third, our inclusion and exclusion criteria did not allow for data collection in all neonates admitted to the NICU during the study period. As described, selection criteria were chosen to identify sick infants who were most likely to have kidney function monitoring, and restrict the number of infants admitted for mild or transient conditions requiring brief periods of supportive care (ie, transient tachypnoea, transient hypoglycaemia, or late prematurity). Given that infants who do not require intravenous fluids rarely have assessments for serum creatinine or quantified urinary output data, restricting these patients reduced the number of infants without adequate data for analysis. Similarly, exclusion of infants who died within the first 48 h of admission is justified because these infants do not always receive full medical support (eg, if the condition is deemed lethal), and 48 h is not ample time to note a rise in serum creatinine and thus be able to assess for AKI. Only 48 (1%) of potential infants were excluded because of death within 48 h. Fourth, despite the large sample size of our study, potential confounders between groups might have been missed. Fifth, we included only two countries outside of North America; thus, this cohort represents mostly North American NICUs. Finally, we did not assess or control for aspects of different health-care systems or seasons (we enrolled infants born from January to March), which might have contributed to variation in antenatal care, mortality rates, and length of stay.

In conclusion, this study provides substantial data depicting the epidemiology of neonatal AKI. We show differences in AKI incidence across gestational age groups and the independent association between AKI and important clinical outcomes. Indeed, our findings are consistent with studies in other critically ill populations, emphasising that the kidney is not just an innocent bystander in critical illness, but rather plays an important role in morbidity and mortality. Initiatives, such as the International Society of Nephrology 0by25 programme,[29] designed to reduce the incidence and sequelae of kidney injury need to also focus on critically ill neonates. Growing evidence on the developmental origin of kidney disease[30] highlights how neonates born premature, small for gestational age, and of low birthweight are at risk of chronic kidney disease because of low nephron number at birth. Low nephron numbers can predispose infants to AKI because they might not have compensatory renal reserve at the time of stress. Furthermore, the effect of AKI on optimal kidney growth in these infants might be substantial. For these reasons, improving understanding of the global burden of neonatal AKI should be a priority for international agencies that advocate for neonates and for populations at risk for kidney disease.

The AWAKEN database will enable the testing of additional questions that cannot be answered in the confines of one publication. Some analyses underway include evaluations of specific AKI risk factors, the effect of fluid balance on outcomes, modifications to the neonatal AKI definition, and the association of AKI with comorbid neonatal conditions. Unfortunately, many questions about neonatal AKI (eg, cause of death, AKI epidemiology during specific events, ability of urine biomarkers to diagnose AKI, and the long-term outcomes after AKI) cannot be addressed in the present cohort because of the retrospective design of the study. To answer these and other questions, partnerships between neonatologists and nephrologists must continue. Carefully planned, adequately powered, prospective studies are greatly needed to further advance our understanding of neonatal AKI. These studies should monitor kidney injury and function data systematically, provide insights about AKI during high-risk events, capture the cause of death, and assess long-term renal recovery. Such studies will provide evidence to create guidelines for neonatologists, paediatricians, and paediatric nephrologists who care for these patients during and after discharge from the NICU.

Contributors

DJA, JGJ, CM, and CSW contributed to the study conception or design. DJA, JGJ, SKS, SW, SR, ASC, RW, CM, JRS, and SS acquired the data. DJA, LJB, and RLG analysed the data. All authors interpreted the data. DJA, JGJ, and LJB drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version to be published.

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