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Original Article

ORIGINAL ARTICLE

Epidemiology of childhood acute kidney injury in England using e-alerts

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ABSTRACT

Background. Few studies describe the epidemiology of childhood acute kidney injury (AKI) nationally. Laboratories in England are required to issue electronic (e-)alerts for AKI based on serum creatinine changes. This study describes a national cohort of children who received an AKI alert and their clinical course.

Methods. A cross-section of AKI episodes from 2017 are described. Hospital record linkage enabled description of AKI-associated hospitalizations including length of stay (LOS) and critical care requirement. Risk associations with critical care (hospitalized cohort) and 30-day mortality (total cohort) were examined using multivariable logistic regression.

Results. In 2017, 7788 children (52% male, median age 4.4 years, interquartile range 0.9–11.5 years) experienced 8927 AKI episodes; 8% occurred during birth admissions. Of 5582 children with hospitalized AKI, 25% required critical care. In children experiencing an AKI episode unrelated to their birth admission, Asian ethnicity, young (<1 year) or old (16–<18 years) age (reference 1–<5 years), and high peak AKI stage had higher odds of critical care. LOS was higher with peak AKI stage, irrespective of critical care admission. Overall, 30-day mortality rate was 3% ($n = 251$); youngest and oldest age groups, hospital-acquired AKI, higher peak stage and critical care requirement had higher odds of death. For children experiencing AKI alerts during their birth admission, no association was seen between higher peak AKI stage and critical care admission.

Conclusions. Risk associations for adverse AKI outcomes differed among children according to AKI type and whether hospitalization was related to birth. Understanding the factors driving AKI development and progression may help inform interventions to minimize morbidity.

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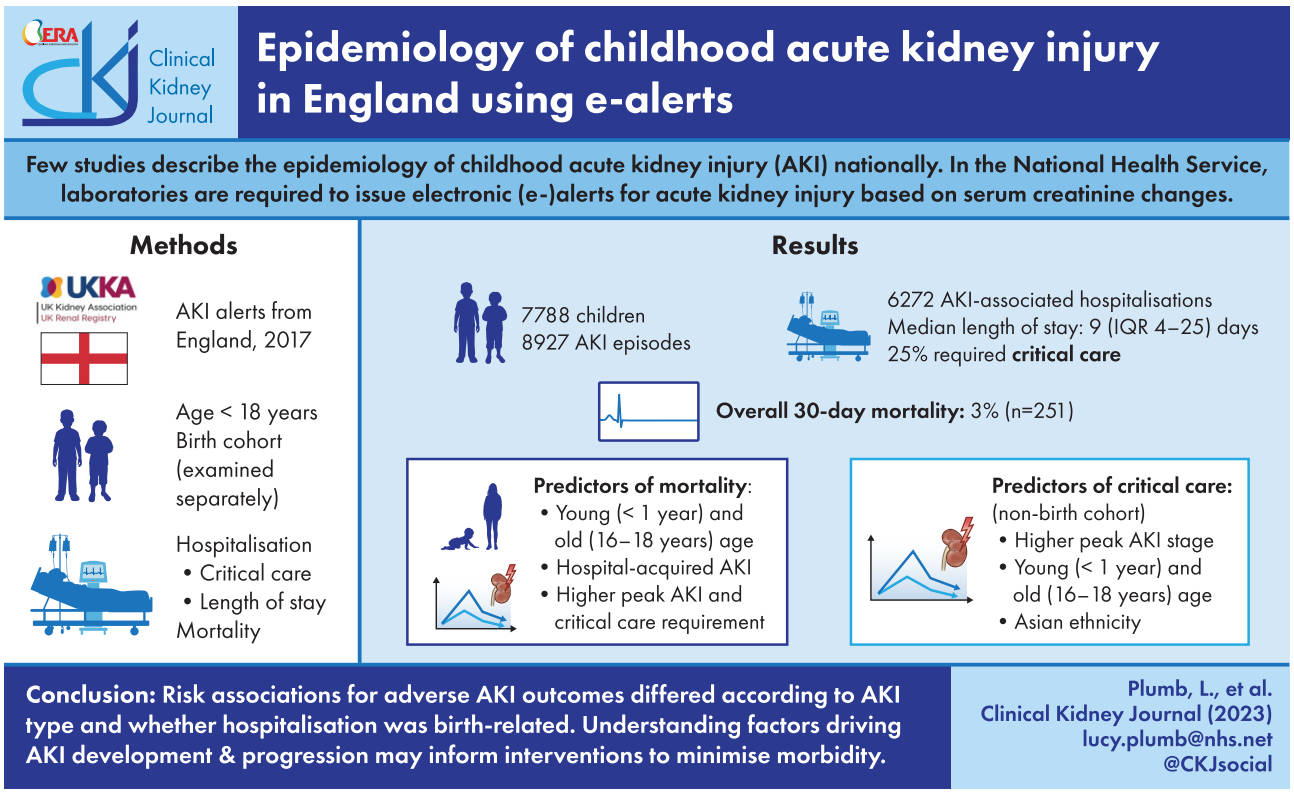
LAY SUMMARY

Acute kidney injury (AKI) is a sudden drop in kidney function. This may have long-term health effects. In England, alerts triggered by rises in a person's blood creatinine levels are sent to the UK Renal Registry. We looked at a 1-year snapshot of alerts for children aged under 18 years across England. We found that children who were very young (under 1 year) or old (16–<18 years) were more likely to need critical care or die during an AKI episode compared with others. Longer length of stay in hospital was seen with increasing AKI alert severity. Children with an AKI alert during their birth admission had the highest risk of needing critical care and death, but this did not relate to AKI severity. This national work has detected factors linked to serious outcomes in AKI; by identifying them, we can now start to address them.

GRAPHICAL ABSTRACT



Keywords: acute kidney injury, children, clinical epidemiology, electronic health records, paediatrics

INTRODUCTION

Acute kidney injury (AKI) confers significant morbidity for hospitalized children including prolonged length of stay (LOS) [1], higher inpatient mortality in critically ill patients [2] and a risk of kidney impairment in the medium-long term [3, 4]. Advances in our understanding of the epidemiology of paediatric AKI have been made in recent years, in part due to a consensus AKI definition from Kidney Disease: Improving Global Outcomes (KDIGO), several large-scale prospective studies [2, 5], and the use of electronic health records to identify and describe populations of interest [6]. However, while the epidemiology of AKI in adults is well described, there are comparatively fewer nationally representative studies in children. Furthermore, while there are large studies of AKI in the critical care setting and among hospitalized, non-critically ill children [7–9], few describe the burden of community-acquired AKI and its outcomes [10, 11].

AKI recognition has been aided by use of clinical alerts. An automated real-time electronic (e-)alert system has been implemented across England and Wales using a rising serum creatinine as a clinical indicator of AKI since 2014 [12, 13]. Using e-alerts, two studies described the epidemiology of childhood AKI in Wales [9, 11]; both highlighted a higher incidence of AKI than previously reported, although variations in 30-day mortality and recovery of kidney function definitions were noted. To our knowledge, no study has used e-alert data with linked hospital data to describe the epidemiology and outcomes of AKI in a national cohort of children. The aims of this study were to describe children in England who received an AKI alert in 2017, to describe complications associated with hospitalized AKI including peak AKI stage, LOS, admission to critical care and 30-day

mortality, and to examine patient and disease factors associated with these outcomes.

MATERIALS AND METHODS

Study design and population

A cross-sectional study was performed to address the study aims. The UK Renal Registry (UKRR) collects data from National Health Service (NHS) laboratories in England issuing AKI e-alerts. The algorithm used to generate e-alerts for AKI, developed by the 'Think Kidneys' working group, aligns with the KDIGO clinical practice guidelines for the detection of AKI (Supplementary data, File S1) [13]. To receive an e-alert for AKI, patients must have a reference serum creatinine available: for children with serum creatinine values available in the preceding 0–7 days, the lowest value was taken as the reference; for children with creatinine values within the preceding 8–365 days, the median value was used for reference. In accordance with the KDIGO AKI staging criteria, stage 1 AKI is a rise in serum creatinine of 1.5–1.9 times the baseline creatinine, stage 2 is an increase of 2.0–2.9 times and stage 3 is a serum creatinine ≥3.0 times the baseline value.

All e-alerts received for children under 18 years between 1 January and 31 December 2017 were examined. Using linkage to the UKRR kidney failure dataset, children on long-term kidney replacement therapy (KRT) were excluded. Alerts solely occurring in the first 3 days of life were excluded as fluctuations in serum creatinine during this time may reflect maternal glomerular filtration rate.

AKI episodes and type

AKI e-alerts were amalgamated into discrete episodes as described previously [14, 15]. Alerts were considered part of a subsequent AKI episode if >30 days passed between e-alerts. Episodes commencing from day 3 of a hospital admission were classified as hospital-acquired AKI (HA-AKI). Episodes beginning outside of hospital, or within the first 2 days of an admission, were classified as community-acquired AKI (CA-AKI); episodes were further sub-categorized as community acquired and admitted (CA-A) or not admitted (CA-NA).

Data collection and linkage

Patient data received with each alert included NHS number, date of birth, sex and postcode, and the serum creatinine value triggering the alert. Using NHS number and date of birth, these data were linked to the Hospital Episode Statistics Admitted Patient Care (HES-APC) dataset, the electronic record of all admissions and inpatient activity occurring at NHS Hospitals in England [16]. HES-APC data were used to describe AKI-associated hospitalizations including primary and co-existing diagnoses at time of hospitalization [16], LOS and need for critical care at the time of or during an AKI episode. The primary diagnosis fields within HES-APC refer to the main condition(s) treated or investigated during the hospitalization during which the AKI episode occurred. One primary diagnosis code is permitted for each finished consultant episode (FCE), representing a continuous period of care under one consultant; hospitalizations however may span more than one FCE and therefore more than one primary diagnosis may be listed. Other listed diagnoses not contained within the primary diagnosis fields are referred to as comorbidities or co-existing diagnoses [16].

Diagnoses within HES were coded using the International Classification of Diseases 10th revision (ICD-10); procedures were coded using the Office for Population Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS-4) criteria [17]. A code list of OPCS procedural codes for KRT (Supplementary data, Table S2) was compiled to examine use in hospitalized children.

Due to potential differences in risk associations, an *a priori* decision was made to stratify hospitalized children according to whether their admission was related to their birth (hereafter known as the 'birth cohort') or not. This cohort was defined as any patient having an admission method code describing the birth of a baby (variable ADMIMETH = 82). Data for infants (<12 months) admitted outside of their birth admission were presented separately. Children who died within 30 days of an AKI episode were identified using the NHS Batch Demographics Service. To support sociodemographic reporting of the patient cohort, socioeconomic deprivation was determined by assigning 2015 English Indices of Multiple Deprivation (IMD) scores to the residential postcode of the patient, which were then grouped into quintiles. The IMD score is derived from Census data and incorporates multiple aspects of deprivation (e.g. housing, employment, crime) to form an ecological measure of relative deprivation [18].

Data analysis

Baseline characteristics are presented for the study cohort, stratified by admission type (birth/non-birth cohort). Odds of critical care (hospitalized children) and mortality (full cohort) were examined using univariable and age- and sex-adjusted multivariable logistic regression models. Risk associations with critical care were based on the first hospitalized AKI episode for each patient; associations with 30-day mortality were based on the first AKI episode for each patient.

Sensitivity analyses

To assess for potential confounding in patients with multiple episodes of AKI, mortality regression analyses were repeated using the last AKI episode in the study period per patient. As other studies have reported similar outcomes [2, 19], AKI stage at start and peak was examined both individually and as stages 2/3 (moderate–severe AKI) combined. Associations with mortality were also examined excluding children who required critical care at the time of, or during their AKI episode. Statistical analyses were conducted using SAS, version 9.4.

RESULTS

The UKRR received data from 125 laboratories on 10115 AKI episodes in 2017 for 8802 children under 18 years; this represents data from 66% of known laboratories in England. Following exclusions, the final cohort comprised 8927 episodes in 7788 children (Fig. 1). The maximum number of episodes per patient was 6; 544 children had more than one hospitalized AKI episode, of which 78 (14%) had multiple episodes during the same admission. Table 1 highlights the baseline characteristics of the study cohort.

AKI alert–associated hospitalizations

A total of 6272 AKI episodes in 5582 children were associated with a hospital admission. Table 2 highlights primary diagnoses

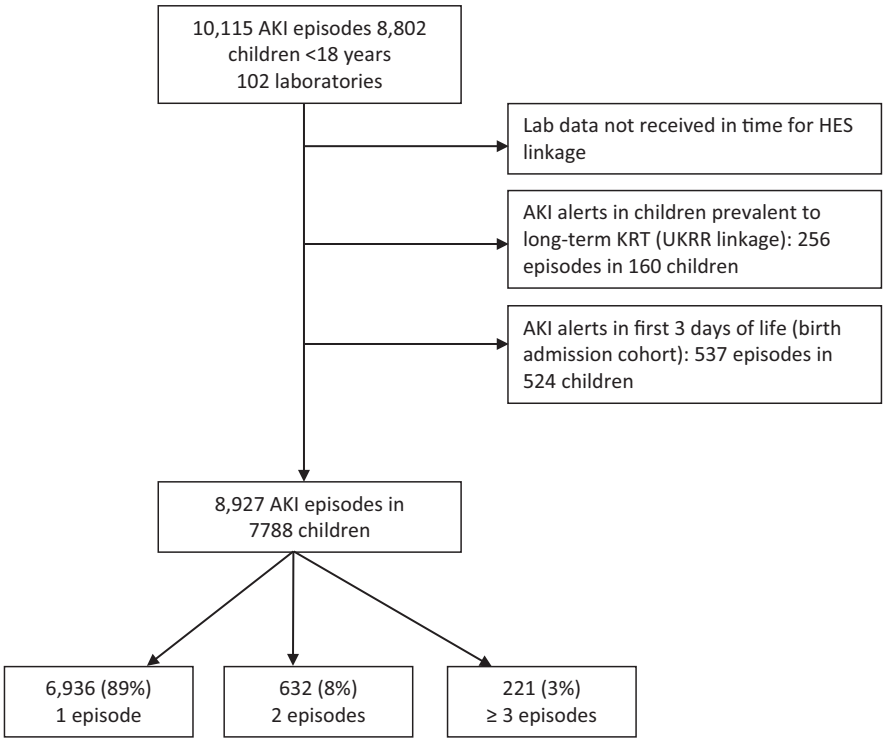


Figure 1: Flow diagram of study cohort and exclusions made.

recorded at the time of first AKI episode. Among the birth cohort, the most common diagnoses were prematurity, followed by genetic or congenital disorders. For the non-birth cohort, frequent primary diagnoses were respiratory disease ($n = 760$, 16%), infections ($n = 611$, 13%), and genetic or congenital disorders ($n = 534$, 11%), with differences seen by AKI type (Supplementary data, Table S3). A primary diagnosis of genitourinary disease was present in <1% of the birth and 7% of non-birth cohorts, respectively.

The most common co-existing diagnoses in the birth cohort at the time of an AKI episode were prematurity ($n = 694$, 98%), congenital or genetic ($n = 431$, 61%) and endocrine/metabolic ($n = 222$, 31%) disorders (Supplementary data, Table S4). For the non-birth cohort, prevalent co-existing diagnoses included respiratory ($n = 1869$, 38%), infections ($n = 1863$, 38%) and endocrine/metabolic disorders ($n = 1660$, 34%); genitourinary disease was noted in 31% ($n = 1527$).

Of the 5582 children hospitalized with an AKI episode, 875 (17%) progressed from AKI stages 1 or 2 to peak stages 2 or 3 (Supplementary data, Table S5). Compared with those with stable AKI, children who progressed were more likely to be younger, require critical care and/or die within 30 days of their AKI episode. No sex, ethnicity or deprivation differences were seen.

At peak, 1163 children (21%) had stage 2 AKI, while 733 (13%) developed stage 3, of whom half had been in stage 3 at the start of the episode (Supplementary data, Table S6). Children with moderate or severe AKI (stages 2 or 3) had a younger median age compared with stage 1 (3 versus 4 years); again, similar distributions of ethnicity and deprivation were seen across peak AKI strata.

A quarter of children who experienced an AKI-associated hospitalization required admission to critical care, either after or at the time of the AKI episode starting (Supplementary data, Table S7). The median age of those requiring critical care was younger (0.7 versus 5 years). Compared with 1- to <5-year-olds, the youngest children [<1 year, adjusted odds ratio (aOR) 4.3, 95% confidence interval (CI) 3.7, 5.1] and those in the oldest age group (16–<18 years, aOR 1.4, 95% CI 1.1, 1.8) had highest odds of requiring admission. Other risk associations included Asian ethnicity (compared with white; aOR 1.5, 95% CI 1.2, 1.8), peak AKI stages 2 (compared with stage 1; aOR 1.5, 95% CI 1.3, 1.7) or 3 (aOR 1.8, 95% CI 1.5, 2.2), and having an AKI episode during birth admission (aOR 2.3, 95% CI 1.8, 2.8; Table 3). Children with CA-AKI episodes that were subsequently hospitalized had lower likelihood of requiring critical care (aOR 0.6, 95% CI 0.5, 0.7) compared with those experiencing HA-AKI. KRT use was recorded in 9% of the critical care cohort, compared with 2% in the remainder. When stratified by birth status, young age (<1 year) remained strongly associated with critical care in the non-birth cohort (aOR 3.0, 95% CI 2.5, 3.6). Higher odds of critical care were also seen by increasing peak AKI stage in this cohort, which were not observed in the birth cohort (Supplementary data, Table S8).

The median LOS for all AKI-associated hospitalizations ($n = 6272$) was 9 (IQR 4–25) days. Episodes observed in the birth cohort had a higher median LOS [37, interquartile range (IQR) 19–72 days], compared with other AKI types (CA-A and HA). Compared with CA-A episodes, HA-AKI was associated with longer LOS (Supplementary data, Table S9). LOS was also higher with peak AKI stage. Critical care admission moderated this association, with higher LOS seen in all AKI types requiring critical care admission compared to episodes without.

Thirty-day mortality (total cohort)

Among 7788 children, 251 deaths were noted (3%); 150 deaths occurred in the hospitalized non-birth cohort (60%), 59 in the birth cohort (24%) and 42 deaths (17%) in children that were not

Table 1: Patient and clinical characteristics of total study cohort, stratified by admission type ($n = 7788$).

			Non-birth cohort	
Variable	Birth cohort	Non-birth cohort	Hospitalized	Not hospitalized
Number of episodes (%)	732 (8)	8195 (92)	5540 (62)	2655 (30)
Number of children	712[a]	7107	4900	2441
% Male	60.1	51.9	51.8	52.1
Median age (years) (IQR)	0 (0.0–0.1)	5 (2–13)	5 (2–12)	6 (3–13)
Age group (years) (%)				
<1	99.7	14	17	8
Of which <1 month	92	4	5	3
Of which 1–12 months	8	10	12	5
1–<5	[b]	33	33	34
5–<11	0	23	22	26
11–<16	0	17	17	19
16–<18	0	13	12	13
Ethnicity[c] (%)				
South Asian	8	9	9	10
Black	5	6	5	7
Other	9	10	10	11
White	78	74	75	73
Missing ($n = 403$)	5	4	2	10
Area level socioeconomic deprivation[c] (%)				
1 (least deprived)	12	14	13	15
2	17	17	17	17
3	20	18	18	17
4	26	22	21	22
5 (most deprived)	25	30	30	30
AKI at start (%)				
Stage 1	79	81	80	84
Stage 2	15	13	14	11
Stage 3	6	6	7	4
AKI peak (%)				
Stage 1	53	72	68	82
Stage 2	28	18	20	13
Stage 3	19	10	12	5
Hospitalization (%)				
Birth	100.0			
CA-A		36	53	
HA		32	47	
CA-NA		32		100

[a]$n = 20$ children experienced one or more AKI episode(s) during their birth admission.
[b]Fewer than five children were born in 2016 and remained hospitalized beyond 1 year of age, when they experienced an AKI episode.
[c]Percentages shown are based on patients with available data; due to small numbers, missing data for socioeconomic deprivation ($n = 46$) are not stratified by admission type. Ethnicity data was enriched with HES ethnicity data therefore there is a higher proportion of patients with missing data among non-admitted cohort. Note: children may be counted more than once since those who experienced an AKI at birth could have a further AKI episode unrelated to their birth.
Cells containing five or fewer patients are suppressed in accordance with NHS Digital's disclosure policy.

hospitalized during their AKI episode. Mortality risk associations are shown in Table 4: children in the youngest age group had 5.5 (95% CI 3.7, 8.0) higher odds of death compared with 1- to <5-year-olds; young people aged 16–<18 years had two-times (aOR 2.0, 95% CI 1.3, 3.3) higher odds of death. No differences were noted by ethnicity or deprivation quintile. Having AKI stage 2 at start had 46% higher odds of mortality compared with stage 1, however there was no evidence of an association with stage 3. Having either moderate (stage 2) or severe AKI (stage 3) at start was associated with 40% higher odds of mortality compared with stage 1 AKI (aOR 1.4, 95% CI 1.1, 1.9) in age- and sex-adjusted models. Incrementally higher odds of death were noted with higher peak AKI stage. Within the hospitalized cohort, episodes associated with a critical care admission had two-times (aOR 2.1, 95% CI 1.5, 2.8, Table 4) higher odds of death compared with those without; associations remained robust when the birth cohort was excluded (aOR 3.0, 95% CI 2.1, 4.2).

Compared with other hospitalized AKI, having CA-A AKI was associated with lower likelihood of death in the univariable model, although in the adjusted model this association was not observed. Community-acquired episodes not requiring admission, however, were associated with 40% lower odds of death compared with any hospitalized episodes (birth, HA or CA-A, 95% CI 0.5, 0.9). Associations and effect estimates were comparable when children from the birth cohort were excluded. Similarly, peak AKI stages 2 and 3 were associated with higher odds of death when children requiring critical care admission, either during or after an AKI episode, were excluded. Findings were unchanged when the last 2017 AKI episode per patient was used.

Table 2: Primary diagnoses listed at time of first AKI-associated hospitalization ($n = 5582$).

	Birth cohort	Non-birth cohort
Number of children	712	4870
Condition, *N* (%)		
Infectious disease		611 (13)
Malignancy		533 (11)
Diseases of circulatory system		193 (4)
Diseases of gastrointestinal system	10 (1)	384 (8)
Diseases of respiratory system	6 (0.8)	760 (16)
Endocrine, nutritional and metabolic diseases		404 (8)
Diseases of nervous system		235 (5)
Prematurity	600 (84)	160 (3)
Congenital and chromosomal abnormalities	155 (22)	534 (11)
Social/mental		26 (0.5)
Disorders of the musculoskeletal system and connective tissue		129(3)
Diseases of genitourinary system		354 (7)
Hepatic disorders		28 (0.6)
Cerebral palsy		
Neural tube defect		
Disorders of the eye and adnexa		
Diseases of the ear and mastoid process		21 (0.4)
Other	7 (1)	955 (20)

Primary and co-existing diagnoses are broadly coded according to ICD-10 disease categories. Cells containing five or fewer patients are suppressed in accordance with NHS Digital's disclosure policy.

Table 3: Crude and age- and sex-adjusted ORs for critical care admission ($n = 5582$).

Variable	Unadjusted OR (95% CI)	Age- and sex-adjusted OR (95% CI)
Female sex	0.8 (0.7, 0.9)	0.9 (0.8, 1.0)
Age group (versus 1–<5 years)		
<1 year	4.4 (3.7, 5.1)	4.3 (3.7, 5.1)
5–<11 years	0.7 (0.5, 0.9)	0.7 (0.5, 0.8)
11–<16 years	0.7 (0.6, 0.9)	0.7 (0.6, 0.9)
16–<18 years	1.4 (1.1, 1.7)	1.4 (1.1, 1.8)
Ethnicity (versus white)		
Asian	1.3 (1.0, 1.6)	1.5 (1.2, 1.8)
Black	0.8 (0.6, 1.1)	0.9 (0.6, 1.2)
Other	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)
Deprivation quintile (versus 5)		
Quintile 1 (least deprived)	1.3 (1.1, 1.6)	1.4 (1.1, 1.7)
Quintile 2	0.9 (0.8, 1.1)	0.9 (0.7, 1.1)
Quintile 3	1.1 (0.9, 1.3)	1.0 (0.8, 1.2)
Quintile 4	1.1 (1.0, 1.4)	1.0 (0.9, 1.2)
AKI stage at start (versus 1)		
Stage 2	1.0 (0.9, 1.2)	1.0 (0.8, 1.2)
Stage 3	0.8 (0.6, 1.1)	0.8 (0.6, 1.0)
AKI stage at peak (versus 1)		
Stage 2	1.7 (1.5, 2.0)	1.5 (1.3, 1.7)
Stage 3	2.0 (1.7, 2.4)	1.8 (1.5, 2.2)
Birth cohort (versus hospitalized, non-birth cohort)	5.7 (4.9, 6.8)	2.3 (1.8, 2.8)
CA-A (versus HA)	0.5 (0.5, 0.6)	0.6 (0.5, 0.7)

Sex estimates are age-adjusted, and age estimates are sex-adjusted.

DISCUSSION

This study describes the burden of AKI in a national cohort of children over a 1-year period, using e-alerts based on international guidance for AKI detection. Children experiencing an AKI alert unrelated to their birth admission demonstrated higher odds of critical care requirement and death in both the youngest (<1 year) and oldest (16–<18 years) age groups. Development of moderate–severe peak AKI stage was associated with higher odds of critical care and death, as was HA-AKI. CA-AKI had lower odds of death within 30 days; admitted patients had lower odds of critical care compared with those with hospital-acquired injury. In children experiencing an AKI episode during their birth admission, high odds of critical care and death were

Table 4: Crude and age- and sex-adjusted ORs for 30-day mortality ($n = 7788$).

Variable	Unadjusted OR (95% CI)	Age- and sex-adjusted OR (95% CI)
Female sex	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)
Age group (versus 1–<5 years)		
0–<1 month	5.5 (3.7, 8.0)	5.5 (3.7, 8.0)
1–12 months	2.4 (1.5, 3.9)	2.4 (1.5, 3.9)
5–<11 years	1.0 (0.6, 1.7)	1.0 (0.6, 1.7)
11–<16 years	1.5 (1.0, 2.5)	1.5 (1.0, 2.5)
16–<18 years	2.0 (1.2, 3.2)	2.0 (1.3, 3.3)
Ethnicity (versus white)		
Asian	1.1 (0.7, 1.8)	1.2 (0.8, 1.9)
Black	1.4 (0.9, 2.4)	1.5 (0.9, 2.5)
Other	1.0 (0.6, 1.5)	1.0 (0.6, 1.6)
Deprivation quintile (versus 5)		
Quintile 1 (least deprived)	0.6 (0.4, 1.0)	0.6 (0.4, 1.0)
Quintile 2	1.0 (0.7, 1.4)	0.9 (0.6, 1.3)
Quintile 3	1.0 (0.7, 1.4)	0.9 (0.6, 1.3)
Quintile 4	1.0 (0.7, 1.5)	1.0 (0.7, 1.4)
AKI stage at start (versus 1)		
Stage 2	1.5 (1.1, 2.1)	1.5 (1.1, 2.1)
Stage 3	1.4 (0.9, 2.3)	1.4 (0.8, 2.2)
Stage 2/3 combined	1.5 (1.1, 2.0)	1.4 (1.1, 1.9)
AKI stage at peak (versus 1)		
Stage 2	2.3 (1.7, 3.1)	2.0 (1.1, 2.7)
Stage 3	3.5 (2.6, 4.9)	3.0 (2.2, 4.1)
Stage 2/3 combined	2.7 (2.1, 3.5)	2.3 (1.8, 3.0)
Non-hospitalized (versus any hospitalized: births, HA, CA-A)	0.5 (0.3, 0.7)	0.6 (0.5, 0.9)
Non-hospitalized (versus hospitalized) excluding birth cohort	0.6 (0.4, 0.8)	0.7 (0.5, 0.9)
CA-A (versus other hospitalized)[a]	0.6 (0.4, 0.8)	0.9 (0.7, 1.3)
Any hospitalized with critical care (versus hospitalized, no critical care)	2.9 (2.2, 3.9)	2.1 (1.5, 2.8)
Any hospitalized with critical care (versus hospitalized, no critical care) excluding birth cohort	3.4 (2.5, 4.8)	3.0 (2.1, 4.2)

[a]CA-NA AKI episodes excluded from analysis.
Sex estimates are age-adjusted, and age estimates are sex-adjusted.

seen compared with the non-birth cohort, although no association was seen between higher peak AKI stage and these outcomes among this cohort.

Based on mid-year population figures [20], we estimate the incidence of children experiencing an AKI episode in 2017 to be 65.6 (95% CI 64.2, 67.1) per 100 000 children. This is higher than previously reported [8, 10, 19], although lower than estimates from the Welsh AKI group using the same methodology [9, 11], and is almost certainly an underestimate due to incomplete national coverage. We noted crude differences in AKI frequency by deprivation quintile and ethnicity; as Wales is relatively more deprived [21] and less ethnically diverse than England [22], differences in population case-mix may account for some of the differences seen.

This study demonstrated that AKI episodes were most frequently seen in the youngest children, as described previously [19]. Using linked hospital data, we were able to differentiate children who had an AKI episode around birth and examine their characteristics and outcomes separately. The male predominance among this cohort may reflect associations between male sex and prematurity [23]. The estimated incidence of AKI was much higher in this cohort at 110.1 (95% CI 102.1, 118.5) children per 100 000 live births. As 97% of births in England occur in a hospital setting and will be captured by hospital records, these data are highly representative [16]. Concerns have been raised regarding the use of changes in serum creatinine to identify AKI in this cohort, given their inherently low values and the relatively small changes required to trigger an e-alert [7, 9]. Due to our reliance on e-alert data to identify AKI episodes, we were unable to incorporate additional parameters as in other studies, such as urine output or independent serum creatinine rises [24], which may result in an underestimation of AKI and risk associations [2]; however, findings that these children were more likely to experience critical care admission, longer LOS and death correlates with other studies [5]. Previously, the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study has shown worse survival for stage 3 AKI in neonates with AKI compared with no/lesser AKI [5], while a single-centre study reported higher proportions of death among neonates with stage 3 AKI compared with stage 2 (19% versus 13.3%) [25]. In contrast to the non-birth cohort, we did not see a graded association between peak AKI stage and odds of critical care or death. While other studies have demonstrated the presence of AKI as an independent risk factor for mortality and prolonged LOS among neonates [5, 24], severity of AKI in this study did not correlate with worsening outcomes.

This observation could contradict a causal relationship between AKI and adverse outcomes or may have occurred due to measurement error and the inherent challenges of quantifying AKI in a newborn cohort. Findings from the AWAKEN study team have previously suggested that absolute rather than relative changes in serum creatinine perform better in predicting adverse outcomes such as mortality, particularly in premature infants, which our birth cohort predominantly comprised of [26].

Contrary to the AWAKEN neonatal cohort, we noted a higher prevalence of prematurity and genetic/congenital disorders, which may be due to differences in eligibility criteria [5], although these diagnoses were noted in other studies [27]. Among the non-birth cohort, few had a kidney disease diagnosis. Our findings contrast those from Norway and Nigeria, where a higher prevalence of kidney disease among children with AKI was described [19, 28]. In this study, co-existing disease was highly prevalent. Previous studies have surmised that a combination of multi-system disease and their treatments are the cause of most AKI, rather than primary kidney disease [8]. Our findings support this theory, meaning that screening for AKI using patient or clinical characteristics associated with progression and/or adverse outcomes including co-existing disease, along with biomarkers [29], may be beneficial. Due to the cross-sectional nature of the study, we cannot comment on diagnoses associated with recurrent AKI.

Risk associations for critical care admission and 30-day mortality were similar. The highest odds of death were seen for the youngest patients, both overall and in the non-birth cohort stratum. Higher odds of critical care and death were also seen among young people aged 16–<18 years compared with 1- to <5-year-olds. Although a relatively high AKI incidence has been noted among older children previously [8], the association with adverse outcomes is new. We speculate this may be due to several factors, including reduced functional kidney reserve in patients with long-standing or complex conditions (74% of the non-birth cohort had more than one co-existing condition listed at the time of their first 2017 AKI-associated hospitalization), or variations in management as children transition to adult services, including differences in the availability, provision and locality of services. It is also possible that peri-pubertal children may be more vulnerable to kidney injury and/or kidney function decline, as has been observed among children with established chronic kidney disease [30, 31]. In the non-birth cohort, worsening peak AKI correlated with higher odds for each outcome, which concurs with findings from the Assessment of Worldwide AKI in Pediatrics, Renal Angina and Epidemiology (AWARE) study [2]. There was some evidence of moderate AKI (stage 2) at start being associated with higher odds of death following AKI, although a similar association was not seen for individuals presenting with stage 3 AKI; due to small numbers, we may have been underpowered to detect an association. The observation that higher LOS was noted with higher peak AKI stage, which is worsened (moderated) by critical care admission, is novel; similarly, progression of AKI was associated with longer LOS, higher critical care requirement and 30-day mortality, suggesting interventions targeting AKI progression may reduce LOS and morbidity. The finding that associations between moderate–severe peak AKI and 30-day mortality are not wholly due to critical care admission provides further evidence that AKI is associated with risks in non-critically ill children, and that early identification and intervention may help improve outcomes. A recent randomized trial of e-alerts in combination with a complex intervention did not reduce mortality in adult patients [32] but led to a reduction in AKI duration and LOS, which equated to healthcare cost savings [33]. A pragmatic clinical trial is now needed to understand whether the same benefits are possible for children.

The strengths of this study include the capture of AKI data on a national level and linkage to several datasets which helped refine the study cohort, describe hospitalized episodes and investigate outcomes stratified by birth admission. Limitations must also be acknowledged: several laboratories did not submit e-alert data and therefore findings will underestimate the true prevalence. Use of AKI e-alerts is reliant on a baseline creatinine value which may mean episodes are missed if a single result is not repeated. Furthermore, alerts may be triggered by artefactual rises, although this is likely to account for a small proportion of alerts. Reliance on a 'baseline' creatinine value in neonates is also problematic when physiological declines in creatinine are expected postnatally. To account for this phenomenon, we excluded any alerts occurring solely in the first 3 days, although this may miss acute injury that would be identified from a 'lack of serum creatinine drop' [34] as well as any cases that occur according to KDIGO definitions [35]. Other factors such as changing volume status, gestational age and muscle mass may effect creatinine values during the initial postnatal period which may result in misclassification of AKI [34].

Use of AKI e-alerts using KDIGO definitions is more sensitive than other definitions [35], particularly for stage 1 AKI where relatively small creatinine changes are required to trigger an alert. Due to the nature of hospital records, factors such as drug use which may be implicated in AKI development and/or progression could not be evaluated. Reliance on diagnoses and procedures from electronic health records may also introduce misclassification bias which may occur at any stage of the coding process, from diagnosis (clinician failing to accurately record problem) to recording (errors in coding diagnosis and processing data). While HES data quality controls have demonstrated improvements in coding accuracy, this will not influence diagnostic error [36]. Finally, although we present age- and sex-adjusted effect estimates, there is the possibility of residual confounding.

In conclusion, a high burden of childhood AKI is seen in England. Understanding the processes that cause AKI development and progression, particularly in high-risk groups, will inform interventions which may help minimize morbidity and may be of cost benefit. Linkage of e-alert data to registry and hospital datasets will support future work to study variations in AKI recognition and care and evaluate long-term kidney outcomes.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

All authors conceived and designed the study. L.P. and A.C. analysed the data. L.P. wrote the manuscript. All authors contributed to manuscript revisions.

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by the UK Renal Registry (AKI data) and NHS Digital (Hospital Episode Statistics data) under license/by permission. Data will be shared on request with permission of the UK Renal Registry and NHS Digital.

CONFLICT OF INTEREST STATEMENT

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NephroCan's CE-certified products are trusted by healthcare professionals around the world. Our commitment to quality and safety is reflected in our operations and processes, which ensure our products provide patients with the best hemodialysis treatment throughout their ESRD journey.

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NephroCan offers a wide range of products and services that cover the "A to Z" of the hemodialysis spectrum. This broad portfolio provides integrated solutions and comprehensive treatments for dialysis patients with various medical needs.

2. Commitment to innovation

NephroCan is committed to innovation and invests heavily in research and development to create new products that can improve patient outcomes. Our focus is to develop products and technologies that will better serve the healthcare industry in the coming years.

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