AKI in Hospitalized Children: Epidemiology and Clinical Associations in a National Cohort

Scott M. Sutherland,* Jun Ji,† Farnoosh H. Sheikhii, Eric Widen,§ Lu Tian,§ Steven R. Alexander,* and Xuefeng B. Ling†

Summary

Background and objectives Although AKI is common among hospitalized children, comprehensive epidemiologic data are lacking. This study characterizes pediatric AKI across the United States and identifies AKI risk factors using high-content/high-throughput analytic techniques.

Design, setting, participants, & measurements For the cross-sectional analysis of the 2009 Kids Inpatient Database, AKI events were identified using International Classification of Diseases, Ninth Revision, Clinical Modification codes. Demographics, incident rates, and outcome data were analyzed and reported for the entire AKI cohort as well as AKI subsets. Statistical learning methods were applied to the highly imbalanced dataset to derive AKI-related risk factors.

Results Of 2,644,263 children, 10,322 children developed AKI (3.9/1000 admissions). Although 19% of the AKI cohort was ≤1 month old, the highest incidence was seen in children 15–18 years old (6.6/1000 admissions); 49% of the AKI cohort was white, but AKI incidence was higher among African Americans (4.5 versus 3.8/1000 admissions). In-hospital mortality among patients with AKI was 15.3% but higher among children ≤1 month old (31.3% versus 10.1%, P<0.001) and children requiring critical care (32.8% versus 9.4%, P<0.001) or dialysis (27.1% versus 14.2%, P<0.001). Shock (odds ratio, 2.15; 95% confidence interval, 1.95 to 2.36), septicemia (odds ratio, 1.37; 95% confidence interval, 1.32 to 1.43), intubation/mechanical ventilation (odds ratio, 1.2; 95% confidence interval, 1.16 to 1.25), circulatory disease (odds ratio, 1.47; 95% confidence interval, 1.32 to 1.65), cardiac congenital anomalies (odds ratio, 1.2; 95% confidence interval, 1.13 to 1.23), and extracorporeal support (odds ratio, 2.58; 95% confidence interval, 2.04 to 3.26) were associated with AKI.

Conclusions AKI occurs in 3.9/1000 at-risk US pediatric hospitalizations. Mortality is highest among neonates and children requiring critical care or dialysis. Identified risk factors suggest that AKI occurs in association with systemic/multiorgan disease more commonly than primary renal disease.
Materials and Methods

Data Sources

This study used the 2009 Kids’ Inpatient Database (KID) (24), an all-payer, inpatient care database for children in the United States that contains information included in a typical discharge abstract. Each patient record contains up to 25 International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) discharge diagnosis codes and 15 ICD-9-CM procedure codes. The KID also contains all patient-refined, diagnosis-related group data, which allow for patients across similar diagnostic groups to be compared from a case complexity standpoint (25). The 2009 KID contains data on 3,391,934 discharges from 4121 hospitals in 44 states that occurred between January 1, 2009 and December 31, 2009. Because this study analyzed deidentified, publically available data, the Stanford Institutional Review Board considered it exempt (May 22, 2012).

Cohort Optimization

Cohort optimization is shown in Figure 1. To identify pediatric hospitalizations at risk for AKI, we excluded patients >18 years, uncomplicated births, patients with ESRD, and renal transplant recipients. Uncomplicated births were excluded using the HOSPBRTH=1 and UNCBRTH=1 variables, because by definition, they could not have been diagnosed with AKI; also, the KID undersamples this subset. Newborns experiencing complications were not excluded (HOSPBRTH=1 and UNCBRTH=0). Patients with ESRD were excluded using the ICD-9-CM codes 585.6 (ESRD), V56.31 (encounter for hemodialysis adequacy testing), V56.32 (encounter for peritoneal dialysis adequacy testing), V56.1 (fitting and adjustment of extracorporeal catheter), and V56.2 (fitting and adjustment of peritoneal dialysis catheter); these patients receive chronic dialysis and are not at risk for AKI. Renal transplant recipients were excluded using the ICD-9-CM codes V42.0 (kidney replaced by transplant) and 996.81 (complications of transplanted kidney), because these elevations in serum creatinine likely represent episodes of allograft dysfunction. Patients were excluded if either of these codes was present as a primary or secondary diagnosis.

Identification of AKI Events

AKI was identified using ICD-9-CM codes 585.5–585.9: 584.5 (acute kidney failure with lesion of tubular necrosis), 584.6 (acute kidney failure with lesion of renal cortical necrosis), 584.7 (acute kidney failure with lesion of renal medullary [papillary] necrosis), 584.8 (acute kidney failure with other specified pathologic lesion in kidney), and 584.9 (acute kidney failure unspecified). Hospitalizations were considered to have been complicated by AKI if any of these codes appeared in any of 25 diagnosis categories.

AKI Subcategories

Neonatal AKI represents a unique spectrum of disease (26), and therefore, the AKI cohort was subdivided; hospitalizations among children ≤1 month of age were classified as neonatal AKI, and hospitalizations among children >1 month of age were classified as pediatric AKI. AKI hospitalizations were subclassified by need for renal replacement therapy. AKI requiring dialysis (AKI-D) was identified using ICD-9-CM codes for hemodialysis/hemofiltration (39.95) and peritoneal dialysis (54.98). Patients carrying both an AKI code and either dialysis code were considered AKI-D. AKI hospitalizations with concomitant critical care (AKI-ICU) were identified using ICD-9-CM critical care codes (27) for mechanical ventilation (96.70–96.72), arterial BP monitoring (89.61), and central venous pressure monitoring (89.62). The presence of one or more of these codes, which serve as surrogate markers of intensive care, resulted in categorization as AKI-ICU.

Figure 1. | Cohort optimization. Patients >18 years old were excluded to create a cohort representative of pediatric disease. Uncomplicated births (by Kids’ Inpatient Database [KID] definition) and patients with ESRD (receiving chronic dialysis) are not at risk for AKI. Creatinine elevations in renal transplant recipients are likely to represent a diagnosis other than AKI (allograft dysfunction).
The KID contains deidentified data; thus, it is not possible to distinguish individual patients, and some admissions likely represent rehospitalizations. Therefore, for all results, the units of analysis are hospitalizations rather than patients. Because of the discharge sampling strategy of the KID, the data must be weighted to permit analyses on data that had been weighted according to the nationally representative estimates; all analyses were performed on data that had been weighted according to the standard Agency for Healthcare Research and Quality procedure (24). Weighted results were subjected to comparative testing between AKI and non-AKI cohorts as well as AKI subgroups using statistical learning strategies; a predictive model was created to accurately determine the KID data elements that were highly associated with an AKI diagnosis. We used prediction analysis of microarrays (PAM), which is commonly applied to high-feature datasets such as DNA microarrays; PAM determines the data elements or features that best contribute to the predictive model or characterize individual classes/cohorts (28,29). Clinical Classification Software codes (286 diagnosis and 231 procedural codes) were used to bin ICD-9-CM codes (n=6722) and analyzed by PAM. PAM identified relevant AKI predictors and eliminated irrelevant data elements, which constitute noise. Subsequently, the data were subjected to machine learning/pattern recognition predictive modeling analyses using linear discriminant analysis (http://www.r-project.org/libraryMASS). Linear discriminant analysis maximizes the ratio of between-class variance to within-class variance, guaranteeing maximal separation between the AKI and non-AKI classes. At the outset, the data were randomly divided into a training dataset (two thirds of the records) and a testing/validation dataset (one third of the records); the training data were used to design the prediction model, and the testing/validation data were used to confirm its accuracy. The results of this analysis are presented as unadjusted odds ratios (ORs). Notably, the datasets are class-imbalanced, because one class (non-AKI) contains significantly more subjects than the other class (AKI). Thus, repeated random subsampling (n=100) was integrated with a voting mechanism to derive the final classification result. Receiver Operating Characteristic (ROC) analysis was performed (30,31) to evaluate the performance of the model. Area under the ROC curve was calculated using ROCR package (30). ORs of the PAM-selected features were computed using generalized

### Data and Statistical Analyses

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### Table 1. Demographics of AKI and non-AKI hospitalizations

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>AKI Cohort</th>
<th>Non-AKI Cohort</th>
<th>P Value</th>
<th>Standardized Difference of the Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (interquartile)</td>
<td>10.8 (1.0–16.8)</td>
<td>2.0 (0–12.8)</td>
<td>&lt;0.001</td>
<td>0.50</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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</tr>
<tr>
<td>Girls (%)</td>
<td>43.6</td>
<td>49.5</td>
<td>&lt;0.001</td>
<td>0.12</td>
</tr>
<tr>
<td>Boys (%)</td>
<td>56.4</td>
<td>50.5</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (%)</td>
<td>49.2</td>
<td>50.6</td>
<td>&lt;0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>African American (%)</td>
<td>20.1</td>
<td>17.4</td>
<td>&lt;0.001</td>
<td>0.07</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>20.1</td>
<td>22.4</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Asian/Pacific Islander (%)</td>
<td>3.2</td>
<td>3.1</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Native American (%)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td>0.00</td>
</tr>
<tr>
<td>Other (%)</td>
<td>6.4</td>
<td>5.5</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Hospital type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children’s hospital (%)</td>
<td>66.2</td>
<td>34.6</td>
<td>&lt;0.001</td>
<td>0.67</td>
</tr>
<tr>
<td>Nonchildren’s hospital (%)</td>
<td>33.8</td>
<td>65.4</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Hospital size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large (%)</td>
<td>69.8</td>
<td>64.4</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Medium (%)</td>
<td>20.8</td>
<td>25.0</td>
<td>&lt;0.001</td>
<td>0.10</td>
</tr>
<tr>
<td>Small (%)</td>
<td>9.4</td>
<td>10.6</td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

When given, the percentage represents the percentage of hospitalizations with available data. The number of patients available for analysis in the AKI and non-AKI cohorts, respectively, are as follows: age (9663 and 2,359,501), gender (10,315 and 2,618,318), race (8515 and 2,233,926), hospital type (9027 and 2,375,714), hospital size (9225 and 2,455,973).
linear modeling (http://www.r-project.org/ library) and EpiCalc (http://cran.r-project.org/doc/contrib/Epicalc_Book.pdf) methods.

**Results**

**AKI Demographics**

The hospitalized population at risk for AKI included 2,644,263 pediatric admissions (Figure 1); 10,322 patients were diagnosed with AKI, yielding an incidence of 0.39% (95% confidence interval [95% CI], 0.38 to 0.40%) or 3.9 cases per 1000 admissions. Demographic data are shown in Table 1. The median age of the AKI cohort was 10.8 years (interquartile range [IQR]=1.0–16.8). This age was higher than patient age for hospitalizations not complicated by AKI (median=2.0 years, IQR=0.1–12.8, P<0.001). One third of AKI events occurred in children 15–18 years of age (Figure 2A). Children ≤1 month of age represented a large proportion of the cohort (19%); however, the incidence of AKI was lowest among this age group. AKI incidence increased in parallel with age (Figure 2A) and was greatest in 15–to 18-year-old patients (6.6 events per 1000 hospitalizations). AKI was more common in boys (56.4% versus 43.6%), whereas non-AKI hospitalizations showed equal sex distribution (50.5% versus 49.5%, P<0.001). African Americans had a greater representation among AKI admissions (20.1% versus 17.4%, P<0.001) whereas Hispanic children were less represented among AKI hospitalizations (20.1% versus 22.4%, P<0.001). Nearly one half of the AKI population was white; however, AKI incidence was highest among African Americans at 4.5 events per 1000 admissions (Figure 2B). Most AKI admissions occurred at large hospitals (69.8%, 2.1 events per 1000 hospitalizations) (Figure 3A) and children’s hospitals (66.2%, 5.6 events per 1000 hospitalizations) (Figure 3B). Of these demographic characteristics, only age and hospital type had an SDM greater than 0.2 (Table 1).

**Case Complexity and Severity of Illness**

Data regarding case complexity and disease severity are shown in Table 2. Compared with non-AKI hospitalizations, at discharge, AKI hospitalizations had more diagnoses listed (median=11, IQR=7–15 versus median=3, IQR=2–5; P<0.001), were considered to suffer from more chronic conditions (median=3, IQR=1–4 versus median=0, IQR=0–1; P<0.001), and had undergone significantly more procedures (median=3, IQR=0–8, versus median=1, IQR=0–2; P<0.001). Based on all patient-refined, diagnosis-related group data, hospitalized children with AKI experienced significantly greater morbidity and mortality risk (Table 2). Among AKI hospitalizations, 96.4% experienced at least a major loss of function, and 59.4% experienced an extreme loss of function; these results are compared with 15.1% and 2.7%, respectively, among non-AKI hospitalizations (P<0.001). Moreover, although only 1.0% of non-AKI hospitalizations qualified as having an extreme likelihood of dying, 46.4% of AKI hospitalizations were classified as having an extreme likelihood of dying (P<0.001). All of these variables, with the exception of moderate likelihood of dying and moderate loss of function, had an SDM>0.8.

**Outcomes**

Outcomes are shown in Figure 4. Hospitalizations complicated by AKI experienced a mortality rate of 15.3% compared with a mortality rate of 0.6% among non-AKI hospitalizations (P<0.001). Mortality within the AKI cohort was significantly higher in neonates than children >1 month of age (31.3% versus 10.1%, P<0.001); 34.5% of AKI hospitalizations required critical care (AKI-ICU) during their stay (71.6% patients ≤1 month versus 23.4% patients >1 month, P<0.001), and mortality was higher in AKI-ICU hospitalizations (32.8% versus 9.4%, P<0.001). Dialysis was required in 8.8% of AKI cases (AKI-D) and used more commonly in children >1 month of age (9.8% versus 4.3%, P<0.001). AKI-D hospitalizations experienced higher mortality (27.1% versus 14.2%, P<0.001).

Length of stay (LOS) data showed a trend similar to the trend seen for mortality (Figure 4). AKI was associated with a prolonged median LOS (9 versus 2 days, P<0.001). Median LOS was longer among neonates (29 versus 7 days, P<0.001), AKI requiring dialysis (21 versus 8 days, P<0.001), and AKI-ICU (29 versus 6 days, P<0.001).

**Factors Associated with the Diagnosis of AKI**

AKI-associated clinical factors are shown in Table 3. In hospitalizations among children >1 month of age (n=7848), liver disease (OR, 1.24; 95% CI, 1.18 to 1.28), respiratory failure (OR, 1.21; 95% CI, 1.17 to 1.25), and pulmonary collapse/pulmonary inflammation (OR, 1.15; 95% CI, 1.11 to 1.19) were associated with AKI. Likewise, shock (OR, 2.15; 95% CI, 1.95 to 2.36), septicemia (OR, 1.37; 95% CI, 1.32 to 1.47), and coagulation disorders (OR, 1.23; 95% CI, 1.18 to 1.28) were associated with AKI. Procedural associations included intubation and mechanical ventilation (OR, 1.2; 95% CI, 1.16 to 1.25), vascular catheterization (OR, 1.18; 95% CI, 1.14 to 1.22), delivery of enteral/parenteral nutrition (OR, 1.14; 95% CI, 1.09 to 1.19), and blood transfusions (OR, 1.11; 95% CI, 1.08 to 1.15). The analysis also identified several factors likely to be a result of AKI rather than a potential cause; these factors included hypertension, anemia, and electrolyte abnormalities (P values<0.001). In hospitalizations among children ≤1 month of age (n=1815), a similar pattern emerged (Table 3). However, the analysis also identified circulatory diseases (OR, 1.47; 95% CI, 1.32 to 1.65), congenital cardiac disease (OR, 1.18; 95% CI, 1.13 to 1.23), and postoperative complications (OR, 1.42; 95% CI, 1.24 to 1.63) as being associated with neonatal AKI. The procedural factors in this cohort also highlight extracorporeal membrane oxygenation and intraoperative bypass (OR, 2.58; 95% CI, 2.04 to 3.26) and operating room vascular procedures (OR, 2.07; 95% CI, 1.78 to 2.41) as associated with AKI. The overall predictive model for AKI in hospitalizations among children ≤1 and >1 month of age resulted in ROC areas under the curve of 0.94 and 0.98, respectively.

**Discussion**

This study represents the most extensive epidemiologic description of AKI among hospitalized children in the United States. Across 2,644,263 hospitalizations
Figure 2. | AKI patient demographics and incident rates. AKI analysis by (A) age and (B) race. Each percent figure represents the percentage of the entire AKI cohort. Additionally, AKI incidence (AKI events per 1000 hospitalizations) is shown from lowest to highest.

Figure 3. | AKI hospital demographics and incident rates. AKI analysis by (A) hospital size and (B) hospital type. Each percent figure represents the percentage of the entire AKI cohort. Additionally, AKI incidence (AKI events per 1000 hospitalizations) is shown from lowest to highest.
encompassing all hospital sizes, types, and acuities, a wide range of disease severities, and both critical and noncritical care populations, we found a national AKI incidence of 3.9 cases per 1000 admissions. Studies using highly sensitive creatinine-based definitions, such as the Acute Kidney Injury Network (AKIN) and Pediatric Risk, Injury, Failure, Loss, and End Stage Renal Disease criteria (pRIFLE), in selective, high-risk populations have found higher...
incidences; rates of 17.9%–52% have been seen in the ICU or after corrective cardiac surgery (5,9,32). However, our findings are comparable with those findings of a single-center study, which used similar diagnostic criteria (4.6–9.9 per 1000 hospitalizations) (2).

The large scale of our study allowed identification of novel AKI demographics in children. The incidence of AKI was highest among African Americans; although AKI has been shown to be more common among African-American adults (1,33), this study is the first study to show this pattern in children. Additionally, AKI was associated with boys. This finding has also been seen among adults (1) but never established in pediatrics. Finally, increasing age was associated with rising AKI incidence; the greatest incidence was among 15–18 year olds. This finding is in contrast with several small studies, which found younger

<table>
<thead>
<tr>
<th>Diagnosis category associations</th>
<th>Patients &gt;1 Mo of Age</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>Associated Factor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock</td>
<td>2.15 (1.95 to 2.36)</td>
<td>Condition due to external cause</td>
<td>Condition due to external cause</td>
<td></td>
</tr>
<tr>
<td>Septicemia</td>
<td>1.37 (1.32 to 1.43)</td>
<td>Severe sepsis</td>
<td>Severe sepsis</td>
<td></td>
</tr>
<tr>
<td>Liver diseases</td>
<td>1.24 (1.18 to 1.28)</td>
<td>Liver diseases</td>
<td>Liver diseases</td>
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<tr>
<td>Coagulation/bleeding disorders</td>
<td>1.23 (1.18 to 1.28)</td>
<td>Circulatory disease</td>
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<tr>
<td>Thrombocytopenia</td>
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<td>Complication of surgical care</td>
<td>Complication of surgical care</td>
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<tr>
<td>Disseminated intravascular coagulation</td>
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<td>Bleeding complicating procedure</td>
<td>Bleeding complicating procedure</td>
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<tr>
<td>Coagulation defect not otherwise specified</td>
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<td>Cardiac surgical complication</td>
<td>Cardiac surgical complication</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1.21 (1.17 to 1.25)</td>
<td>Postoperative infection</td>
<td>Postoperative infection</td>
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<tr>
<td>Hypertension</td>
<td>1.2 (1.14 to 1.27)</td>
<td>Fluid/electrolyte disorders</td>
<td>Fluid/electrolyte disorders</td>
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<tr>
<td>Pulmonary collapse/pleurisy</td>
<td>1.15 (1.11 to 1.19)</td>
<td>Perinatal conditions not otherwise specified</td>
<td>Perinatal conditions not otherwise specified</td>
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<tr>
<td>Anemia</td>
<td>1.1 (1.07 to 1.12)</td>
<td>Neonatal arrhythmia</td>
<td>Neonatal arrhythmia</td>
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<tr>
<td>Fluid/electrolyte disorders</td>
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<td>Neonatal dehydration</td>
<td>Neonatal dehydration</td>
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<tr>
<td>Nutritional/endocrine/metabolic disorders</td>
<td>1.05 (1.03 to 1.07)</td>
<td>Cardiac congenital anomalies</td>
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<td>Disorder phosphorous metabolism</td>
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<td>Respiratory distress syndrome</td>
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<tr>
<td>Hypocalcemia</td>
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<td>Disorder of magnesium metabolism</td>
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<tr>
<td>Condition caused by external cause</td>
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<td>Severe sepsis</td>
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<td>Sepsis</td>
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<tr>
<td>Hypoxemia</td>
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<tr>
<td>Procedural category associations</td>
<td>Intubation/mechanical ventilation</td>
<td>Extracorporeal circulatory support</td>
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<tr>
<td>Vascular catherization</td>
<td>1.18 (1.14 to 1.22)</td>
<td>Extracorporeal membrane oxygenation</td>
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<td>Parenteral/enteral nutrition</td>
<td>1.14 (1.09 to 1.19)</td>
<td>Extracorporeal membrane oxygenation for cardiac surgery</td>
<td>Extracorporeal membrane oxygenation for cardiac surgery</td>
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<tr>
<td>Blood transfusion</td>
<td>1.11 (1.08 to 1.15)</td>
<td>Operating room procedure on vessel</td>
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<tr>
<td></td>
<td></td>
<td>Occlusion of thoracic vessel</td>
<td>Occlusion of thoracic vessel</td>
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<td>Arterial suture</td>
<td>Arterial suture</td>
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<td>Resection of thoracic vessel</td>
<td>Resection of thoracic vessel</td>
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<td>Blood transfusion</td>
<td>Blood transfusion</td>
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<td>Parenteral/enteral nutrition</td>
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</tr>
</tbody>
</table>

Table 3. Unadjusted AKI associations
age to be associated with greater AKI risk (9,34,35). Although the overall incidence of AKI among infants ≤1 month of age was lower than in other age groups, they comprised approximately 20% of the entire AKI cohort, despite the fact that they represent less than 0.5% of the age span studied. Although our study suggests that AKI is not necessarily common across the massive neonatal population, neonatal AKI clearly represents a substantial proportion of the total pediatric AKI burden. Of note, many of the studies referenced above used creatinine-based AKI definitions rather than ICD-9-CM coding. Because younger children tend to have lower serum creatinine values, smaller absolute changes can result in an AKI diagnosis when using the creatinine-based definitions. Additionally, given the lower initial creatinine values, it is possible that clinicians, many of whom use less objective AKI definitions in practice, still interpret creatinines that have technically increased to normal in smaller children.

Our study also offers a broad description of AKI-associated outcomes. Children whose hospitalizations were complicated by AKI experienced a mortality rate of 15.3%. Subgroup analysis suggests that this mortality is driven by neonatal AKI (31.2%), AKI-ICU (32.8%), and AKI-D (27.1%). The substantial mortality seen among neonates with AKI is consistent with previously published data (36–38). Likewise, ICU-associated AKI has been associated with higher mortality rates (5,11). Perhaps more importantly, our study suggests that children with non-ICU AKI experience a reduced but nontrivial mortality rate of 9.4%. Notably, LOS followed an identical pattern to mortality, with longer stays seen in children ≤1 month of age, patients needing dialysis, and children with concomitant critical care.

Our study also shows the heightened case complexity and health risks associated with AKI. Hospitalizations complicated by AKI had significantly more diagnoses, chronic conditions, and procedures documented at discharge. Furthermore, patients with AKI were over 20 times more likely to experience an extreme loss of function and over 40 times more likely to experience an extreme likelihood of dying. Additionally, our ensemble learning analysis revealed a striking pattern; all of the diagnostic and procedural AKI associations identified by the predictive model emphasized the multiorgan system nature of pediatric AKI and highlighted the frequent need for critical care. The study provides strong evidence for the prevailing notion that, in the current hospital setting, children are developing AKI because of systemic disease, injury to other organ systems, and treatment required to manage these disease states rather than primary renal disease (20,23,34). Among children >1 month of age, shock and sepsis were highly associated with AKI. The same is true of liver disease, respiratory failure, and mechanical ventilation. Not surprisingly, nearly one quarter of AKI hospitalizations received concomitant intensive care. This figure reached 70% among children ≤1 month of age, establishing the ICU as the primary setting for neonatal AKI. Although sepsis, liver disease, and mechanical ventilation were also associated with neonatal AKI, the analysis highlighted the link between cardiac disease/surgery and AKI in this population (9,26).

It is important to interpret these findings in the context of their limitations. One limitation is our reliance on ICD-9-CM codes for AKI diagnosis. The use of standard, staged definitions, such as in RIFLE (39), pRIFLE (40), AKIN (41), and Kidney Disease Improving Global Outcomes (KDIGO) (42) studies, will likely improve future analyses. However, we feel that the limitations associated with ICD-9-CM codes, the use of which is necessary for analysis of the KID, are outweighed by the ability to generate such a large, comprehensive AKI cohort. Notably, although the use of ICD-9-CM codes has yet to be validated in children, this approach has been successfully used in adults (43–45). Validating these codes in children is an important subsequent step in pediatric AKI research. Also, unique patient identifiers are not present in the KID. Thus, it was not possible to identify and eliminate readmissions. Another limitation is the lack of a temporal relationship between discharge data elements. It is not possible to determine if a diagnosis of sepsis occurred before or after a diagnosis of AKI; thus, it is challenging to define AKI causality in this study, and it was not possible to control for additional risk factors in patients with AKI. However, the innovative design of the analysis did allow us to identify significant AKI associations, which we reported in lieu of AKI cause. This same issue also limited our ability to determine the location where AKI occurred. Although we feel that the inclusion of intensive care procedure codes was successful in differentiating ICU-associated AKI from general care AKI, it is possible that we did not capture all such patients.

In summary, this study represents the largest epidemiologic description of pediatric AKI to date. Use of a large discharge database and an innovative ensemble learning approach allowed us to describe the incidence, demographics, outcomes, and associations for pediatric AKI across the United States. Future studies using the same analytic strategy with the granular, temporally related data available within the electronic medical record and standard AKIN/pRIFLE/KDIGO definitions will allow more accurate assessment of AKI causality and development of AKI predictive strategies, and they may lead to improved pediatric AKI-related care.

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Disclosures

None.

References
