Patterns of acute kidney injury and functional outcome scores in pediatric patients hospitalized with acute respiratory failure

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Abstract

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Background

Acute kidney injury (AKI) is diagnosed in up to 30% of children admitted to pediatric intensive care units (PICU) and is strongly associated with morbidity and mortality. In recent years, there has been an increased focus on patient-centered outcomes and quality of life among survivors of AKI. One study of pediatric sepsis patients with AKI found that AKI was independently associated with worsened functional status (FS) among survivors. The present investigation focused on functional outcomes of critically ill children with acute respiratory failure (ARF) and concurrent AKI.

Objectives

1. Describe the frequency of AKI in children diagnosed with acute respiratory failure (ARF).
2. Determine association between AKI among children with ARF and worsened FS after PICU stay among survivors.

Design/Methods

This was a single-center retrospective study at a tertiary care PICU that included children aged 3 months-18 years admitted to the PICU from 01/2013-10/2020 with ARF requiring mechanical ventilation. ARF was defined as a primary or secondary visit diagnosis that was listed in the electronic health record (EHR) during the first three days of the index PICU admission. Children who died during the first three days of PICU admission were excluded (n=13). AKI was defined using KDIGO serum creatinine (SCr) criteria. Severe AKI was defined as AKI Stage 2/3. Pediatric Cognitive Performance Category (PCPC) and Pediatric Overall Performance Category (POPC) scores from pre-PICU baseline and PICU discharge were compared. New substantive morbidity was defined as an increase in PCPC or POPC by ≥1 point.

Results

The final analysis included 324 patients. Severe AKI was present in 19.7% of patients. Among survivors (92%), new substantive PCPC morbidity was seen in 8.3% of children with severe AKI, compared to 1.7% in those with no AKI. New substantive POPC morbidity was also more common in survivors with severe AKI compared to no AKI (20.8% vs 13.6%, respectively). After adjusting for age and initial illness severity (PRISM-III, excluding SCr), the association between severe AKI and new substantive functional morbidity among survivors was reduced (adjusted risk difference 5.5%; 95% CI -8.4%-19.3%). PICU mortality was higher in patients with severe AKI compared to no AKI (25.0% vs 6.9%, respectively) and this association also was slightly weakened after adjustment (adjusted risk difference 16.1%; 95% CI 4.6%-27.6%).

Conclusions

AKI is commonly seen in children with ARF and is strongly associated with PICU mortality. In our study, there was a suggestion that AKI also was independently associated with worsened FS at time of PICU discharge, but this result was statistically imprecise. Further research using more granular scales, such as the Functional Status Score, may be needed to better elucidate this relationship.

Background

Acute kidney injury (AKI) is associated with increased morbidity and mortality in pediatric patients,[1,2] and early identification and management of AKI is crucial for improving outcomes.[3] Starr et al. found that severe AKI is associated with an increased risk of death and new morbidity after pediatric septic shock, including new organ failure and prolonged length of stay in the intensive care unit.[4]

Pediatric acute respiratory failure (ARF) is a common reason for admission to the pediatric ICU (PICU), with more than 42,000 children (17.6% of all PICU admissions) receiving mechanical ventilation in the United States annually.[5] The cumulative incidence of AKI during hospitalization of pediatric patients with ARF ranges from 20-50%.[6] There is a growing body of literature suggesting that in pediatric patients with ARF, concurrent AKI is associated with increased mortality.[7–10]

In recent years, there has been increasing attention given to quality-of-life related measures in patients with AKI.[4] One study of pediatric patients who required continuous kidney replacement therapy observed worsened functional status at time of PICU discharge.[11] However, the impact of AKI on functional status in pediatric patients with ARF has not been well studied.

The aims of this study were to describe the frequency of AKI in children diagnosed with ARF, and to determine whether there is an independent association between AKI and worsened functional status at the time of PICU discharge among survivors. We hypothesized that AKI would have an independent association with worsened functional status after PICU stay among survivors.

Methods

We conducted a retrospective, single center cohort study of children admitted to Seattle Children's PICU between 1/1/2013 and 10/1/2020. Patient data were obtained from the EHR and Seattle Children's Virtual Pediatric Systems™ (VPS) database. This study was approved by Seattle Children's Institutional Review Board (STUDY00003622).

Inclusion Criteria

All patients aged 3 months to 18 years with their first admission to the PICU with a clinical diagnosis of ARF requiring invasive mechanical ventilation were eligible for inclusion. To minimize the potential for immortal time bias,[12] only subjects who survived to the end of the third day of PICU admission were included.

Exclusion Criteria

Patients identified as requiring PICU admission after a surgical intervention or as a result of traumatic injury were excluded from the study. In addition, patients admitted to the PICU with a primary neurologic diagnosis, history of chronic kidney disease stage 4/5, dialysis, kidney transplant, or a tracheostomy which was present at the time of PICU admission were also excluded.

Pediatric ARF

STAR Code (VPS' proprietary diagnosis classification) 518.5 was used to screen for any diagnosis of ARF or acute respiratory distress syndrome. STAR Code 518.5 is classified as 'Pulmonary Insufficiency/Shock Lung, Adult Respiratory Distress Syndrome (ARDS), Acute Hypoxic Respiratory Failure (AHRF), Acute Lung Injury (ALI),' which corresponds to ICD-9 Code 518.81 'Acute Respiratory Failure' and ICD-10 Code J9600

'Acute respiratory failure, unspecified whether with hypoxia or hypercapnia.' Date ranges of invasive mechanical ventilation were determined using documentation in the VPS database and were matched to the encounter ID of the PICU admission of interest. As described above, those with visit diagnoses unrelated to underlying lung pathology were excluded to best capture a cohort with respiratory failure secondary to true lung pathology. Those with a tracheostomy present prior to PICU admission were not eligible for inclusion because of their pre-existing respiratory condition. Highest Oxygenation Saturation Index (OSI) during the first three days of PICU admission was calculated and the incidence of Extracorporeal Membrane Oxygenation (ECMO) was quantified.

Exposure

The primary exposure was AKI (which was defined using Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine (SCr) criteria[13]) diagnosed during the first three days of PICU admission, and was dichotomized as either no AKI (defined as no/stage 1 AKI) or severe AKI (defined as stage 2/3 AKI). When available, baseline SCr was used and was defined as the mean of all SCr measurements over the 365 days immediately preceding the PICU admission of interest. When baseline SCr data was not available, a baseline SCr was back-calculated using the Bedside Schwartz Equation where it was assumed the subject had a normal baseline estimated glomerular filtration rate of 100 mL/min/1.73 m^2.

Outcomes

The primary outcome measure was new substantive morbidity among survivors, which was defined as an increase in Pediatric Cognitive Performance Category (PCPC) score or Pediatric Overall Performance Category (POPC) score of at least 1 point from pre-PICU baseline to time of PICU discharge or day 28 of PICU admission, whichever was earlier. PICU mortality was considered only following the first three PICU days, allowing for a comparison of outcomes in children with and without AKI that was not biased as a result of deaths occurring before some cases had the potential to be diagnosed with AKI. A composite outcome of PICU mortality or new substantive morbidity was also evaluated.

Statistical methods

Continuous data were described using median and interquartile range, and categorical data with counts and percentages. Pearson's Chi-squared tests were used for tests of association among categorical variables, and Wilcoxon Rank Sum tests were used for tests of association among ordinal variables. Assessment of the association of AKI status in the first three days of PICU admission with the outcomes of PICU mortality and new substantive morbidity among survivors was done using binary logistic regression. A generalized linear model with Gaussian distribution was used to calculate risk differences. Standard errors were corrected with sandwich estimators. All generalized linear models were adjusted for age category in years (<1, 1-11, >= 12) and Pediatric Risk of Mortality-III (PRISM-III) score (excluding SCr) at time of PICU admission. A patient's age in years was highly collinear with height and weight, and so height and weight were not included in the final models. We did not adjust for highest Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score (excluding SCr) during the first 28 days of PICU admission because it was presumed that organ dysfunction during the admission was mediated by the presence or absence of AKI.

All statistical analyses were performed using R version 4.2.3 (RStudio 2023.03.0).

Results

Overall, 438 children were eligible for inclusion, and all had PCPC/POPC scores available at pre-PICU baseline and PICU discharge. Of those eligible, 82 (18.7%) were excluded for lack of SCr result during the PICU admission. Another 19 (4.3%) were excluded because no recorded height was available to back-calculate a baseline SCr, and 13 (3.0%) were excluded because they died within the first three days of PICU admission.

The final analysis included 324 children, of whom 104 (32.1%) had baseline SCr available, and the rest had it back-calculated as described above (Figure 1).

Severe AKI

Prior to limiting severe AKI events to those which occurred in the first three days of PICU admission, all first time AKI events in the study population were analyzed (Figure 2). Severe AKI events overwhelming occurred in the first three days of PICU admission (64 events in the first three days vs 18 events after day three). Severe AKI was diagnosed in 64/324 (19.7%) of children. It was more likely to occur in older subjects (median age 6.1 years, vs 1.8 years in no AKI group; p<0.001) (Table 1). Baseline PCPC scores in children who developed severe AKI were not statistically different than those who did not develop AKI (p=0.523). In contrast, baseline POPC scores of the severe AKI group were statistically higher than those of the no AKI group (p=0.005).

PICU mortality

PICU mortality was higher in patients with severe AKI compared to no AKI (25.0% vs 6.9%, respectively; p<0.001) (Table 2). This association persisted but was slightly weakened after adjustment for age category and PRISM-III score (excluding SCr) (adjusted risk difference 16.1%; 95% CI 4.6%-27.6%).

Other PICU Outcomes

Among all subjects, severe AKI was also associated with fewer ventilator-free PICU days (median 21.0 days vs 23.0 days; p=0.002) and longer PICU length of stay (median 10.5 days vs 7.0 days; p=0.001).

Hospital Outcomes

Among all subjects, severe AKI was associated with a longer overall hospital length of stay (median 28.0 days vs 15.5 days; p<0.001). Among survivors (290/324; 92%), severe AKI was also associated with a longer overall hospital length of stay (median 21.5 days vs 15.0 days; p=0.002). Return to renal baseline—defined as a last SCr that was less than 0.3 mg/dL and less than 1.5 times above baseline creatinine by time of hospital discharge—was seen in 48.9% of survivors with severe AKI.

Functional outcomes

Among survivors, new substantive PCPC morbidity was seen in 8.3% of those with severe AKI compared to 1.7% in no AKI (p=0.028). New substantive POPC morbidity was also more common in survivors with severe AKI (15.6% vs 13.6% in no AKI; p=0.200). The composite outcome of new substantive morbidity

was more common in survivors with severe AKI (18.8% vs 13.6% in no AKI; p=0.047). After adjusting for age and PRISM-III score (excluding SCr), the size of this association was diminished (adjusted risk difference 5.5%; 95% CI -8.4%-19.3%). Among all subjects, the composite outcome of PICU mortality or new substantive morbidity was more common in subjects with severe AKI (43.8% vs 19.6% in no AKI; p<0.001). This association persisted but was slightly weakened after adjustment for age and PRISM-III score (excluding SCr) (adjusted risk difference 17.7%; 95% CI 3.7%-31.7%).

Discussion

In this study, severe AKI occurred in 19.7% of children with ARF. Those with severe AKI had higher PICU mortality after controlling for age and illness severity at time of PICU admission. These findings are consistent with prior literature of AKI in pediatric ARF.[4,6–10] Biologic mechanisms underpinning this association between AKI and mortality in children with lung injury likely include a fluid overloaded state, acidosis, and upregulation of inflammatory pathways.[14]

In this cohort, there was a suggestion that survivors of pediatric ARF who experienced AKI were more likely to have worsened cognitive and overall functional outcomes than survivors without AKI (as assessed by the PCPC and POPC, respectively), but the difference was modest and plausibly the result of chance. In contrast, a prior study by Starr et al. observed that pediatric sepsis patients with AKI were more likely to have new functional morbidity than those without AKI.[4] One explanation for this may be that the functional outcome scoring systems (PCPC/POPC) used in this study are less sensitive at detecting small changes in functional status than the scoring system used by Starr et al (Functional Status Scale).[15] AKI associated with lung injury and sepsis may also be distinct subphenotypes that may affect overall and cognitive functioning in different ways, albeit the most common organ dysfunction in sepsis is pulmonary.[16,17] One recent study of pediatric ARDS patients found new functional morbidity was common after PICU admission and that after adjusting for severity of illness, severity of ARDS category was not a risk factor for new functional morbidity.[18] It should be noted that this study used the Functional Status Scale and did not analyze the association of AKI with new functional morbidity.

Limitations of this study include the small study population and the single center nature of this study. Additionally, while illness severity was controlled for with PRISM-III score, there may still be differences in underlying illness/physiology that could not be controlled for adequately. The functional outcome scoring system used in this study is not the most sensitive tool for detecting subtle changes in functional status,[15] and so it is possible that this is the reason why little difference in functional status was detected in either the severe AKI and no AKI group. Lastly, no urine output data was collected in this study, which may have led to an underestimation of the true incidence of AKI in this cohort, particularly in infants and young children.[19]

Knowledge of whether there are new functional morbidities in patients with AKI may lead to more directed therapies in patients with AKI during and after PICU admission, such as more intensive occupational and physical therapy. Understanding the new morbidities children experience after suffering AKI would also further support the need for earlier detection and treatment of AKI, with the goal of preventing or lessening these new morbidities from occurring in this patient population. We suggest that future functional outcome research involving AKI should utilize the newer Functional Status Score when possible, as we have demonstrated that new cognitive and overall functional morbidities after AKI may be subtle and therefore difficult to detect using less sensitive scoring scales. We also

suggest that this work be expanded outside of ARF to include other disease processes known to commonly result in AKI, with the goal to determine whether those who suffer AKI from other etiologies have negative effects in their functional performance after hospital admission.

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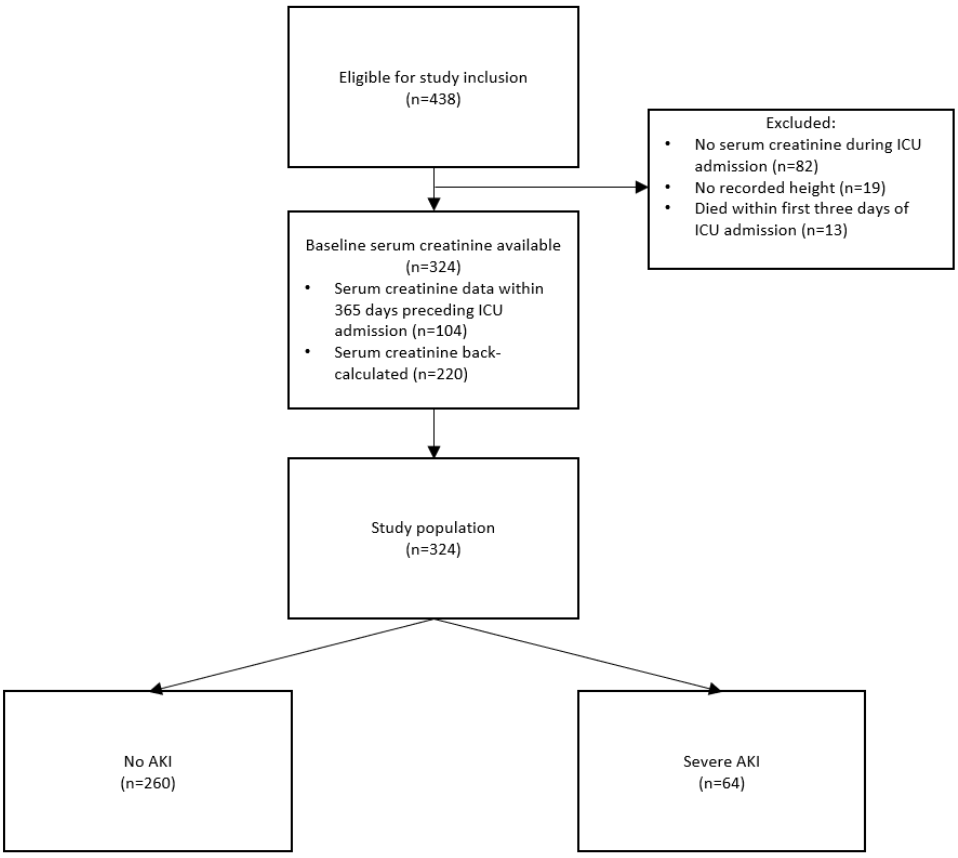

Figure 1. Flow diagram describing the selection process of the study population.

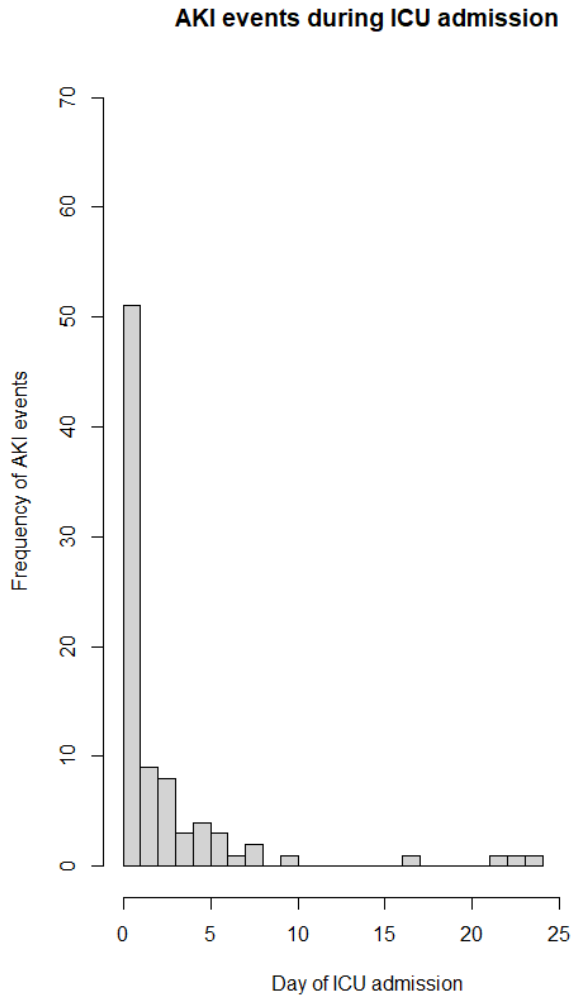

Figure 2. Frequency of first AKI event of PICU admission for each subject in the study population by day of PICU admission. Note, AKI events were considered only if they occurred within the first three days of PICU admission.

Table 1. Demographic and Baseline Characteristics of Study Population by AKI status

Demographic and Baseline Characteristics	Absent/Stage 1 AKI (n = 260)	Stage 2/3 AKI (n = 64)	p
Male, n (%)	144 (55.4)	42 (65.6)	0.138[a]
Age (yr), median (IQR)	1.8 (0.6-6.4)	6.1 (2.1-12.0)	<0.001[b]
Race, n (%)			
White or Caucasian	124 (47.7)	27 (42.2)	0.515[a]
Black or African American	30 (11.5)	3 (4.7)	0.164[a]
Asian	21 (8.1)	14 (21.9)	0.003[a]

American Indian or Alaskan Native	11 (4.2)	2 (3.1)	0.962[a]
Native Hawaiian and Other Pacific Islander	11 (4.2)	0 (0)	0.198[a]
Multiracial	0 (0)	1 (1.6)	0.447[a]
Other	47 (18.1)	14 (21.9)	0.605[a]
Unknown or not reported	16 (6.2)	3 (4.7)	0.881[a]
Ethnicity, n (%)			
Hispanic	61 (23.5)	19 (29.7)	0.383[a]
Not Hispanic	186 (71.5)	41 (64.1)	0.311[a]
Unknown or not reported	13 (5.0)	4 (6.3)	0.929[a]
Height at PICU admission (cm), median (IQR)	82.0 (67.0-114.8)	118.2 (78.9-144.0)	<0.001[b]
Weight at PICU admission (kg), median (IQR)	11.7 (8.1-21.6)	26.1 (11.3-45.2)	<0.001[b]
PRISM-III Score (excluding SCr), median (IQR)	4.0 (0.8-9.0)	12.0 (5.0-18.3)	<0.001[b]
Highest OSI[c], median (IQR)	18.9 (12.5-25.8)	20.7 (17.1-31.4)	0.025[b]
Highest OSI classification[d]			0.080[e]
Mild/Moderate	62 (23.8)	8 (12.5)	
Severe	186 (71.5)	54 (84.4)	
Unknown/Missing	12 (4.6)	2 (3.1)	
Highest PELOD-2 Score (excluding SCr)[f], median (IQR)	8.0 (6.0-11.0)	12.0 (9.8-15.0)	<0.001[b]
Extracorporeal Membrane Oxygenation[g], n (%)	17 (6.5)	9 (14.1)	0.068[a]
PCPC (pre-PICU baseline), n (%)			0.523[e]
Normal (1)	223 (85.8)	56 (87.5)	
Mild disability (2)	16 (6.2)	4 (6.3)	
Moderate disability (3)	19 (7.3)	4 (6.3)	
Severe disability (4)	2 (0.8)	0 (0)	
Coma or vegetative state (5)	0 (0)	0 (0)	
POPC (pre-PICU baseline), n (%)			0.005[e]
Good overall performance (1)	133 (51.2)	19 (29.7)	
Mild overall disability (2)	44 (16.9)	13 (20.3)	
Moderate overall disability (3)	77 (29.6)	32 (50.0)	
Severe overall disability (4)	6 (2.3)	0 (0)	
Coma or vegetative state (5)	0 (0)	0 (0)	

AKI = acute kidney injury, IQR = interquartile range, PRISM-III = Pediatric Risk of Mortality Score, SCr = serum creatinine, OSI = Oxygenation Saturation Index, PELOD-2 = Pediatric Logistic Organ Dysfunction-2 Score, PCPC = Pediatric Cerebral Performance Category (scored 1-6 where 6 = death), POPC = Pediatric Overall Performance Category (scored 1-6 where 6 = death)

[a] Pearson's Chi-squared test without Yates Continuity Correction or Fisher's Exact test

[b] Wilcoxon rank sum test

[c] Highest OSI during first three days of PICU admission

[d] Highest OSI classification during first three days of PICU admission using the Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) criteria for stratification of pediatric acute respiratory distress syndrome severity: mild/moderate (OSI < 16), severe (OSI ≥ 16)[20]

[e] Cochran-Armitage test for trend

[f] Highest PELOD-2 score (excluding SCr) during the first 28 days of PICU admission

[g] Extracorporeal Membrane Oxygenation during PICU admission

Table 2. Unadjusted Outcomes of Interest by AKI Status

Outcomes	Absent/Stage 1 AKI (n = 260)	Stage 2/3 AKI (n = 64)	p
PICU mortality, n (%)	18 (6.9)	16 (25.0)	**<0.001**[a]
New substantive morbidity, n (%) - among survivors	33 (13.6)	12 (18.8)	**0.047**[a]
PICU mortality or New substantive morbidity, n (%)	51 (19.6)	28 (43.8)	**<0.001**[a]
Ventilator-free days[b], median (IQR)	23.0 (16.0-26.0)	21.0 (0.0-24.0)	**0.002**[c]
PICU length of stay (d), median (IQR)	7.0 (4.0-14.0)	10.5 (6.0-17.5)	**0.001**[c]
Hospital length of stay (d), median (IQR)	15.5 (7.0-37.5)	28.0 (14.0-67.3)	**<0.001**[c]
PCPC (PICU discharge), n (%)			**<0.001**[d]
Normal (1)	205 (78.8)	39 (60.9)	
Mild disability (2)	17 (6.5)	6 (19.4)	
Moderate disability (3)	17 (6.5)	3 (4.7)	
Severe disability (4)	3 (1.2)	0 (0)	
Coma or vegetative state (5)	0 (0)	0 (0)	
Brain death or death (6)	18 (6.9)	16 (25.0)	
POPC (PICU discharge), n (%)			**<0.001**[d]
Good overall performance (1)	103 (39.6)	8 (12.5)	
Mild overall disability (2)	58 (22.3)	19 (29.7)	
Moderate overall disability (3)	76 (29.2)	21 (32.8)	
Severe overall disability (4)	5 (1.9)	0 (0)	
Coma or vegetative state (5)	0 (0)	0 (0)	
Brain death or death (6)	18 (6.9)	16 (25.0)	
Survived to PICU discharge			
Total, n (%)	242 (93.1)	48 (75.0)	-
New substantive PCPC morbidity, n (%)	4 (1.7)	4 (8.3)	**0.028**[a]
New substantive POPC morbidity, n (%)	33 (13.6)	10 (15.6)	0.200[a]
Ventilator-free days, median (IQR)	23.5 (19.0-26.0)	23.0 (18.8-25.0)	0.239[c]
PICU length of stay (d), median (IQR)	6.0 (4.0-12.0)	10.0 (6.0-16.0)	**0.002**[c]
Hospital length of stay (d), median (IQR)	15.0 (7.0-36.0)	21.5 (14.0-64.5)	**0.002**[c]

Return to renal baseline[e], n (%)	-	23 (48.9)	-

AKI = acute kidney injury, IQR = interquartile range, PCPC = Pediatric Cerebral Performance Category, POPC = Pediatric Overall Performance Category

[a] Pearson's Chi-squared test without Yates Continuity Correction or Fisher's Exact test

[b] Ventilator-free days were defined as the number of days the patient was alive and free of mechanical ventilation. In the case of 28 ventilator-free days, a patient is given a value of 0 if they die before day 28 or are still receiving mechanical ventilation at day 28.[21]

[c] Wilcoxon rank sum test

[d] Cochran-Armitage test for trend

[e] Return to renal baseline was considered as a last serum creatinine that was less than 0.3 mg/dL and less than 1.5 times above baseline creatinine by time of hospital discharge. One survivor in the Severe AKI group did not have follow-up serum creatinine.

Table 3. Adjusted Associations Between Severe AKI Diagnosed in the First Three Days of PICU Admission and Outcomes of Interest

Outcomes	Adjusted Effect (95% CI)	Adjusted risk difference (95% CI)	p
PICU mortality		16.1% (4.6%, 27.6%)	**0.006**
New substantive morbidity - among survivors		5.5% (-8.4%, 19.3%)	0.440
PICU mortality or New substantive morbidity		17.7% (3.7%, 31.7%)	**0.013**

All outcomes shown are after adjustment for age category in years (<1, 1-11, >= 12) and PRISM-III score (excluding serum creatinine).