# The Incidence of Acute Kidney Injury and Its Effect on Neonatal and Pediatric Extracorporeal Membrane Oxygenation Outcomes: A Multicenter Report From the Kidney Intervention During Extracorporeal Membrane Oxygenation Study Group

Geoffrey M. Fleming, MD[1]; Rashmi Sahay, PhD[2]; Michael Zappitelli, MD[3]; Eileen King, PhD[2]; David J. Askenazi, MD[4]; Brian C. Bridges, MD[1]; Matthew L. Paden, MD[5]; David T. Selewski, MD[6]; David S. Cooper, MD, MPH[7]

*See also p. 1186.

[1]Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN.

[2]Division of Biostatistics and Epidemiology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

[3]Department of Pediatrics, McGill University Health Centre, Montreal, QC, Canada.

[4]Department of Pediatrics, University of Alabama Birmingham, Birmingham, AL.

[5]Department of Pediatrics, Emory University, Atlanta, GA.

[6]Department of Pediatrics and Communicable Diseases, University of Michigan School of Medicine, Ann Arbor, MI.

[7]Department of Pediatrics, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

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For information regarding this article, E-mail: Geoffrey.fleming@vanderbilt.edu



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**Objective:** In a population of neonatal and pediatric patients on extracorporeal membrane oxygenation; to describe the prevalence and timing of acute kidney injury utilizing a consensus acute kidney injury definition and investigate the association of acute kidney injury with outcomes (length of extracorporeal membrane oxygenation and mortality).

**Design:** Multicenter retrospective observational cohort study.

**Setting:** Six pediatric extracorporeal membrane oxygenation centers.

**Patients:** Pediatric patients (age, < 18 yr) on extracorporeal membrane oxygenation at six centers during a period of January 1, 2007, to December 31, 2011.

**Interventions:** None.

**Measurements and Main Results:** Complete data were analyzed for 832 patients on extracorporeal membrane oxygenation. Sixty percent of patients had acute kidney injury utilizing the serum creatinine Kidney Disease Improving Global Outcomes criteria ($AKI^{SCr}$) and 74% had acute kidney injury using the full Kidney Disease Improving Global Outcomes criteria including renal support therapy ($AKI^{SCr + RST}$). Of those who developed acute kidney injury, it was present at extracorporeal membrane oxygenation initiation in a majority of cases (52% $AKI^{SCr}$ and 65% $AKI^{SCr + RST}$) and present by 48 hours of extracorporeal membrane oxygenation support in 86% ($AKI^{SCr}$) and 93% ($AKI^{SCr + RST}$). When adjusted for patient age, center of support, mode of support, patient complications and preextracorporeal membrane oxygenation pH, the presence of acute kidney injury by either criteria was associated with a significantly longer duration of extracorporeal membrane oxygenation support ($AKI^{SCr}$, 152 vs 110 hr; $AKI^{SCr + RST}$, 153 vs 99 hr) and increased adjusted odds of mortality at hospital discharge ($AKI^{SCr}$: odds ratio, 1.77; 1.22–2.55 and $AKI^{SCr + RST}$: odds ratio, 2.50; 1.61–3.90). With the addition of renal support therapy to the model, acute kidney injury was associated with a longer duration of extracorporeal membrane oxygenation support ($AKI^{SCr}$, 149 vs 121 hr) and increased risk of mortality at hospital discharge ($AKI^{SCr}$: odds ratio, 1.52; 1.04–2.21).

**Conclusion:** Acute kidney injury is present in 60–74% of neonatal-pediatric patients supported on extracorporeal membrane oxygenation and is present by 48 hours of extracorporeal membrane oxygenation support in 86–93% of cases. Acute kidney injury has a significant association with increased duration of extracorporeal membrane oxygenation support and increased adjusted odds of mortality at hospital discharge. (*Pediatr Crit Care Med* 2016; 17:1157–1169)

**Key Words:** acute kidney injury; acute renal failure; extracorporeal membrane oxygenation; renal dialysis

Extracorporeal membrane oxygenation (ECMO) provides short-term support for patients with refractory cardiac or pulmonary failure. Acute Kidney Injury (AKI) in the critically ill population has been repeatedly demonstrated to be associated with adverse outcomes (1–11). Children treated with ECMO who develop AKI are at increased risk for adverse outcomes with mortality rates ranging from 47% to 100% with a graded increase by stage of AKI (12–26).

The Extracorporeal Life Support Organization (ELSO) collects outcome data for patients supported by ECMO (27). The definition of "renal complication" or AKI used by the registry includes the need for renal support therapy (RST) or a threshold serum creatinine (SCr) greater than 1.5 mg/dL (27). The published proportion of neonatal AKI from the registry ranges from 10% to 22% using SCr data (15, 28–30). The most recent ELSO International Data Summary suggests the proportion of neonatal and pediatric AKI ranges from 1.3% to 13% using a SCr definition, rising to 20–43% when RST is included (27).

The Kidney Disease Improving Global Outcomes (KDIGO) (31) consensus definition utilizes a staged severity classification referenced to change from baseline function or the need for RST to characterize the severity of AKI. These criteria have been shown to predict morbidity and mortality in a stepwise fashion in critically ill children and are suggested to be the standard definition (9, 32). Utilizing older consensus definitions, the single center incidence of AKI in ECMO has been reported to be as high as 72%, with the highest incidence in those infants and neonates with congenital cardiac disease and those with congenital diaphragmatic hernia (25, 26, 33). The incidence of AKI in single center studies of pediatric ECMO patients has been reported to be as high as 58% in broader pediatric populations (20, 22, 34). To date, there has not been a large multicenter study evaluating the KDIGO AKI definition in a broad neonatal and pediatric ECMO population.

The current study is a systematic evaluation of ECMO data from six centers with three specific aims: 1) describe the incidence and timing of AKI utilizing the KDIGO AKI definition; 2) evaluate the impact of the inclusion of RST in the definition on the proportion of patients with AKI; and 3) investigate the association of AKI with outcomes (length of ECMO and mortality) in a multicenter pediatric ECMO population. We hypothesized that AKI defined by the KDIGO AKI criteria would be more prevalent than previously reported and be associated with increased length of ECMO support and mortality.

## METHODS

### Study Design

Study design is a retrospective observational cohort study of all pediatric patients (age, < 18 yr) on ECMO at six centers from January 1, 2007, to December 31, 2011. Investigational Review Board approval for data collection and study was obtained and maintained at each individual participating center.

### Data Sources

Data sources for this study included the ELSO registry (ELSO, Ann Arbor, MI) and data from individual study sites. Individual study sites collected data retrospectively from medical charts and electronic medical records for data not included in the ELSO database, which was entered into a REDCap database (Vanderbilt University, Nashville, TN) (35). The final dataset for the cohort was created by merging data utilizing a four point matching scheme (ELSO ID, date of birth, date ECMO initiation, and date ECMO discontinuation).

### Cohort

Inclusion criteria were all patients less than 18 years old at the time of ECMO initiation at the participating institutions during the study period. Patients with multiple runs of ECMO, defined as two ECMO support events greater than 24 hours apart, were excluded from analysis due to the potential collinearity of AKI developed during the initial run, which may have affected the need for a second ECMO run and/or ultimate survival outcome. Patients with fewer than four variable field matching at data merge were excluded from analysis.

### Data Collection

Data including age at ECMO initiation, weight at hospital admission, gender, and center of ECMO support were collected. Age was categorized as neonates (0–30 d) and pediatric (31 d to 18 yr). Pre-ECMO variables included serum pH, need for vasoactive medication, and oxygenation index (OI). ECMO variables collected included indication for ECMO, support mode (veno-venous or venoarterial) with subclassification of venoarterial if any component of the cannulation included an arterial cannula (veno-arterial venous, veno-venous arterial, etc.), duration of ECMO, and number of nonrenal complications. Date of ECMO initiation and decannulation was used to calculate duration of ECMO, as time difference in hours between ECMO initiation date-time stamp and the date-time stamp for decannulation. Renal specific variables included SCr at baseline, lowest SCr from hospitalization to ECMO initiation, SCr at ECMO initiation, first recorded value daily for the first 21 days of ECMO, and at RST initiation. Baseline SCr was defined as the lowest recorded value in the chart for up to 90 days prior to ECMO initiation. RST included intermittent hemodialysis, peritoneal dialysis, continuous renal replacement therapy, or slow continuous hemofiltration. Date of RST initiation and discontinuation was collected.

### Definition of AKI

AKI was assessed at three time points: pre-ECMO, ECMO initiation to 48 hours, and more than 48 hours on ECMO. AKI

was defined using both the SCr criteria ($AKI^{SCr}$) of the KDIGO definition (31) or the addition of RST ($AKI^{SCr + RST}$) as follows:

Stage 0: Increase SCr less than 0.3 mg/dL from baseline and SCr less than 1.5 times baseline.

Stage 1: (0.3 mg/dL ≤ increase SCr from baseline < 4 mg/dL and SCr < 1.5 times baseline) or (increase SCr < 4 mg/dL from baseline and SCr ≥ 1.5 times baseline and SCr < 2.0 times baseline).

Stage 2: Increase SCr less than 4 mg/dL from baseline and SCr greater than or equal to 2.0 times baseline and SCr less than 3.0 times baseline.

Stage 3: Increase SCr greater than or equal to 4 mg/dL from baseline or SCr greater than or equal to 3.0 times baseline or need for RST ($AKI^{SCr + RST}$)

A patient was categorized for AKI using SCr in the $AKI^{SCr}$ cohort and by the need for RST in the $AKI^{SCr + RST}$ cohort with a concomitant automatic classification of stage 3 disease.

AKI in the neonatal cohort was adjudicated by two members of the research team with expertise in Pediatric Nephrology and AKI (M.Z., D.J.A.); any discrepancy was reviewed with a third team member (D.T.S.). This was done due to difficulties establishing a baseline SCr in the neonatal population (36). The adjudication used the following step-wise criteria based on local expert opinion to define the baseline SCr: 1) lowest SCr prior to maximum SCr; 2) lowest SCr during hospitalization including those measured after maximum SCr; and 3) normative published values for age.

### Outcomes

Outcomes included ECMO duration, mortality at ECMO decannulation, and mortality at hospital discharge. Mortality at ECMO decannulation was defined as death within 24 hours postdecannulation. Mortality by hospital discharge included mortality at ECMO decannulation as well as survival through the ECMO decannulation period but death by hospital discharge.

### Statistical Analysis

Data were summarized for entire cohort and by status and stages of AKI defined by $AKI^{SCr}$ and $AKI^{SCr + RST}$ criteria. Continuous variables were presented as median and interquartile range (IQR), and Wilcoxon signed rank test was used to test for differences between the groups (AKI vs no-AKI) and Kruskal-Wallis test for differences between the stages of AKI. Categoric variables were presented as frequency counts and percentages, and differences between the groups were tested using chi-square/Fisher exact test. Overall incidence of AKI, by the two definitions, was examined at ECMO initiation, less than or equal to 48 hours of ECMO, and greater than 48 hours of ECMO by mode of ECMO and ECMO support type. Univariate linear regression models were developed to identify potential factors associated with ECMO duration, after log transformation of ECMO duration due to positive skewness. Least square (LS) means of the log transformed data and 95% CIs for the LS mean were back transformed resulting in an estimate of the median (95% CI) on the original measurement scale. Significant factors from univariate analysis were then entered into a multivariable analysis to evaluate the association between AKI/no-AKI with ECMO duration. Mode of ECMO support and pH were considered to be important covariates in multivariable analyses. Although RST (yes/no) had a significant effect in univariate analysis, it was included only in the multivariable model examining the effect of $AKI^{SCr}$ due to its inclusion in the definition of $AKI^{SCr + RST}$. Although reported in demographic data, OI was not examined as a covariate due to significant amount of missing data. Association between AKI/no-AKI and mortality at ECMO decannulation (yes vs no) and between AKI/no-AKI and mortality at hospital discharge (yes vs no) was examined using univariate and multivariable logistic regression analysis with and without RST adjustment, as applicable. Results were presented as odds ratio (OR) and 95% CI. All analyses were two-sided and $p$ value less than or equal to 0.05 was considered statistically significant. SAS version 9.4 (SAS Institute, Cary, NC) was used to conduct all analyses.

## RESULTS

### Study Population

During the study period, 1,009 patients underwent ECMO, and complete data were analyzed for 832 patients (**Fig. 1**). The majority of patients was neonates (60%), had a pulmonary indication for ECMO support (56%) with the most common mode of support being venoarterial (73%) (**Table 1**). The severity of illness in the cohort was substantial with a pre-ECMO OI median (IQR) of 45 (28–67), pH 7.2 (7.1–7.3) and 86% requiring vasoactive support. Nearly 89% of patients had a nonrenal complication as tracked in the ELSO registry and had a median (IQR) of 143 (75–260) hours on ECMO. RST was provided in 48% (401/828) of the cohort of whom 97% (389/401) received RST during ECMO and 3% (12/401) prior to ECMO. Of those receiving RST, 23% was delivered via continuous renal replacement therapy machine and 73% via inline hemodiafilter (Table 1).

### AKI Incidence and Demographics

Using the $AKI^{SCr}$ definition, 502 patients (60%) had AKI (169/502 [34%] stage 1, 164/502 [33%] stage 2, and 169/502 [34%] stage 3 disease). **Table 2** contains patient and ECMO variables associated with AKI. Patients with $AKI^{SCr}$ were significantly older with greater body weight. Severity of illness pre-ECMO was not significantly different between the groups as measured by pH and the need for vasoactive support. Patients with $AKI^{SCr}$ were more likely to require ECMO support for cardiac or extracorporeal cardiopulmonary resuscitation indications, have more complications, receive ECMO for a longer duration, and receive RST. There was no association between pre-ECMO severity of illness measures (pH, vasoactive medication) and worsening stage of $AKI^{SCr}$. Patient and ECMO variables associated with $AKI^{SCr}$ by stage of disease are presented in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/PCC/A313).

Using the $AKI^{SCr + RST}$ definition, 615 patients (74%) had AKI (89/615 [14%] stage 1, 65/615 [11%] stage 2, and 461/615 [75%] stage 3 disease). Table 2 contains patient and ECMO variables associated with AKI. Patients with $AKI^{SCr + RST}$ were significantly older and had greater body weight than the group with no AKI.

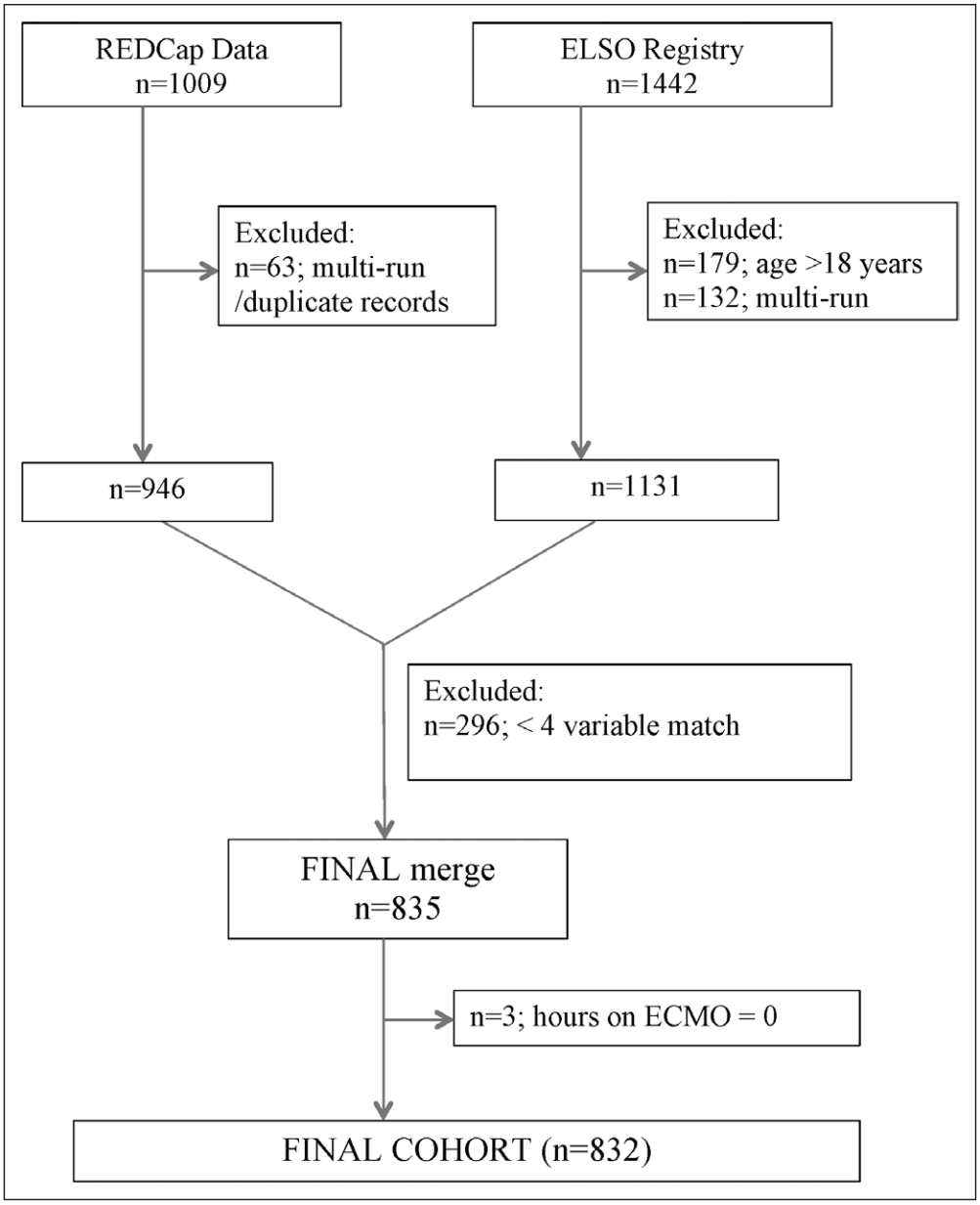


**Figure 1.** Flow diagram for study patients. ECMO = extracorporeal membrane oxygenation, ELSO = Extracorporeal Life Support Organization, REDCap = research electronic data capture.

Severity of illness pre-ECMO was not significantly different between the groups as measured by the need for vasoactive support and not clinically different as measured by pH. Patient and ECMO variables associated with $AKI^{SCr + RST}$ by stage of disease are presented in **Supplemental Table 2** (Supplemental Digital Content 2, http://links.lww.com/PCC/A314).

### Timing of AKI

The cross-sectional incidence of AKI at ECMO initiation in the pediatric cohort ranged from 50% ($AKI^{SCr}$) to 62% ($AKI^{SCr + RST}$), 66% to 82% at 48 hours, and 77% to 88% at greater than 48 hours. New episodes of AKI occurred between initiation and 48 hours of ECMO in 16% ($AKI^{SCr}$) and 20% ($AKI^{SCr + RST}$) of cases, and 11% ($AKI^{SCr}$) and 6% ($AKI^{SCr + RST}$) at greater than 48 hours. Timing of AKI varied by stage and ECMO support indication or ECMO mode for both definitions in the pediatric cohort (**Table 3**). Timing of AKI analysis was not undertaken for the neonatal cohort due to the adjudication process in the definition of AKI and the need to use post-ECMO creatinine as the baseline comparative level.

### Association of AKI With ECMO Outcomes

The overall median (IQR) duration of ECMO was 143 (74,260) hours for the cohort. Duration of ECMO support was significantly longer in patients with AKI regardless of the definition used. In those with $AKI^{SCr}$, the median duration of ECMO was 141.5 hours (95% CI, 129.3–154.9) versus 115.4 (95% CI, 103.1–129.2) ($p = 0.006$) for those without AKI. In patients with $AKI^{SCr + RST}$, the median duration was 137.8 hours (126.9–149.6) versus 111.3 (96.6–128.2) ($p = 0.01$) in those without AKI. Univariate analysis for the association of AKI and non-AKI variables with duration of ECMO is presented in **Table 4**.

Death occurred for 44% (368/830) of the total cohort by hospital discharge, of whom 27% (225/830) died at ECMO decannulation, and 17% (143/830) survived ECMO decannulation but died by hospital discharge. Unadjusted mortality at decannulation and mortality by hospital discharge were significantly increased in patients with AKI regardless of the definition used. The unadjusted OR (95% CI) for mortality at decannulation as compared to no AKI was 1.75 (1.26–2.43) for $AKI^{SCr}$ and 2.55 (1.68–3.88) for $AKI^{SCr + RST}$. The unadjusted OR (95% CI) for mortality by hospital discharge as compared to no AKI was 2.14 (1.60–2.86) for $AKI^{SCr}$ and 3.07 (2.16–4.36) for $AKI^{SCr + RST}$. RST had a significant effect on mortality at both decannulation 2.21 (1.61–3.02) and discharge 2.79 (2.10–3.71). Univariate analysis of AKI and non-AKI variables for the association with mortality at decannulation and by hospital discharge is presented in **Table 5**.

In multivariable analyses, the association of AKI with outcomes was evaluated, adjusting for age, center of support, mode of support, nonrenal complications, and pre-ECMO pH.

**TABLE 1. Patient and Extracorporeal Membrane Oxygenation Demographic Data for the Entire Cohort, Data Presented as *n* (%) Unless Otherwise Specified**

| Variable | *n* | Data |
|---|---|---|
| Age (d), median (IQR) | 832 | 9 (1–221.5) |
| Age category (%) | 832 | |
| Neonates | | 502 (60.3) |
| Pediatric | | 330 (39.7) |
| Gender (%) | 827 | |
| Males | | 487 (58.9) |
| Females | | 340 (41.1) |
| Admission weight (kg), median (IQR) | 830 | 3.6 (3–7) |
| Center (%) | 832 | |
| A | | 213 (25.6) |
| B | | 89 (10.7) |
| C | | 107 (12.9) |
| D | | 183 (22) |
| E | | 226 (27.2) |
| F | | 14 (1.7) |
| Pre-ECMO | | |
| Oxygenation index, median (IQR)[a] | 542 | 45.4 (28.0–66.7) |
| pH median (IQR) | 766 | 7.2 (7.1–7.3) |
| Inotropes (% yes) | 832 | 712 (85.6) |
| ECMO indication (%) | 832 | |
| Pulmonary | | 468 (56.3) |
| Cardiac | | 217 (26.1) |
| Extracorporeal cardiopulmonary resuscitation | | 147 (17.7) |
| ECMO mode (%) | 832 | |
| Venovenous | | 214 (25.7) |
| Venoarterial | | 608 (73.1) |
| Other | | 10 (1.2) |
| Extracorporeal Life Support Organization nonrenal complication (% yes) | 832 | 739 (88.8) |
| ECMO duration (hr), median (IQR) | 832 | 143 (74.5–260) |
| Mortality (% yes) | | |
| At ECMO decannulation | 830 | 225 (27.1) |
| By hospital discharge | 830 | 368 (44.3) |
| RST performed (%) | 828 | |
| Yes | | 401 (48.4) |
| No | | 427 (51.6) |
| RST mode (%) | 822 | |
| Continuous renal replacement therapy | | 94 (11.4) |
| Inline hemodiafilter | | 293 (35.6) |
| Intermittent hemodialysis | | 3 (0.4) |
| Peritoneal dialysis | | 5 (0.6) |
| None | | 427 (51.6) |
| Timing of RST (%) | 828 | |
| None | | 427 (51.6) |
| During ECMO | | 389 (47) |
| Pre-ECMO | | 12 (1.5) |

ECMO = extracorporeal membrane oxygenation, IQR = interquartile range, RST = renal support therapy.

[a]Thirty-three percent of data points for oxygenation index are missing.

In addition, presence of RST was modeled for $AKI^{SCr}$ analysis. The presence of AKI by $AKI^{SCr}$ and $AKI^{SCr + RST}$ criteria showed association with duration of ECMO, even when adjusted for covariates (**Table 6**). Using $AKI^{SCr + RST}$ criteria, the odds for mortality at decannulation with AKI was 1.9 times higher (OR, 1.92 [1.15–3.23]; $p = 0.01$) than those without AKI. The presence of AKI using either definition significantly increased the odds of mortality by hospital discharge (OR, 1.77 [1.22–2.55]; $p = 0.002$) for $AKI^{SCr}$ and (OR, 2.50 [1.61–3.90]; $p < 0.0001$) for $AKI^{SCr + RST}$, compared to no AKI. These results did not change after further adjustment for RST when examining $AKI^{SCr}$.

## DISCUSSION

This study systematically evaluates the KDIGO AKI definition in a broad multicenter cohort of pediatric ECMO patients. There are three important findings from this study. First, the incidence of AKI in the neonatal and pediatric ECMO population is high and affects a majority of ECMO patients with incidence ranging from 60% to 74% depending on the definition used. Second, AKI occurs early in the ECMO course of the pediatric patient, with the majority of those with AKI identified at ECMO initiation and 93% of those identified with AKI by 48 hours. Third, the presence of AKI is associated

**TABLE 2. Demographic Data for Patients by Presence of Acute Kidney Injury**

| Variable | No-AKI$^{SCr}$ ($n = 323$) | AKI$^{SCr}$ ($n = 502$) | $p$ | No-AKI$^{SCr + RST}$ ($n = 207$) | AKI$^{SCr + RST}$ ($n = 615$) | $p$ |
|---|---|---|---|---|---|---|
| Age (d), median (IQR) | 2 (1–18) | 31 (6–415) | < 0.0001 | 2 (1–9) | 20 (4–333) | < 0.0001 |
| Age category (%) | | | < 0.0001 | | | < 0.0001 |
| Neonates | 247 (49.6) | 251 (50.4) | | 168 (33.9) | 328 (66.1) | |
| Pediatric | 76 (23.2) | 251 (76.7) | | 39 (12.0) | 287 (88.0) | |
| Gender (%) | | | 0.03 | | | 0.18 |
| Males | 205 (42.4) | 278 (57.6) | | 130 (27.0) | 351 (73.0) | |
| Females | 117 (34.7) | 220 (65.3) | | 77 (22.9) | 259 (77.1) | |
| Missing = 12 | | | | | | |
| Admission weight (kg), median (IQR) | 3.3 (2.9–4.3) | 3.9 (3–9) | < 0.0001 | 3.3 (2.9–4.1) | 3.8 (3.0–8.4) | < 0.0001 |
| Center city (%) | | | < 0.0001 | | | < 0.0001 |
| A | 45 (21.2) | 167 (78.8) | | 35 (16.5) | 177 (83.5) | |
| B | 27 (31.0) | 60 (69.0) | | 21 (24.7) | 64 (75.3) | |
| C | 72 (67.3) | 35 (32.7) | | 66 (61.7) | 41 (38.3) | |
| D | 72 (40.2) | 107 (59.8) | | 19 (10.6) | 160 (89.4) | |
| E | 103 (45.6) | 123 (54.4) | | 64 (28.4) | 161 (71.6) | |
| F | 4 (28.6) | 10 (71.4) | | 2 (14.3) | 12 (85.7) | |
| Pre-ECMO | | | | | | |
| pH, median (IQR) | 7.2 (7.1–7.3) | 7.2 (7.1–7.3) | 0.40 | 7.2 (7.1–7.3) | 7.2 (7.1–7.3) | 0.05 |
| Inotropes (% yes) | 284 (87.9) | 423 (84.3) | 0.14 | 183 (88.4) | 522 (84.9) | 0.21 |
| ECMO indication (%) | | | < 0.0001 | | | < 0.0001 |
| Pulmonary | 247 (52.9) | 220 (47.1) | | 167 (36.0) | 297 (64.0) | |
| Cardiac | 50 (23.5) | 163 (76.5) | | 26 (12.2) | 187 (87.8) | |
| Extracorporeal cardiopulmonary resuscitation | 26 (17.9) | 119 (82.1) | | 14 (9.7) | 131 (90.3) | |
| ECMO mode (%) | | | < 0.0001 | | | < 0.0001 |
| Venovenous | 128 (60.1) | 85 (39.9) | | 82 (38.9) | 129 (61.1) | |
| Venoarterial | 192 (31.9) | 410 (68.1) | | 124 (20.6) | 477 (79.4) | |
| Other | 3 (30) | 7 (70) | | 1 (10) | 9 (90) | |
| Extracorporeal Life Support Organization nonrenal complication (% yes) | 257 (79.6) | 477 (95.0) | < 0.0001 | 148 (71.5) | 583 (94.8) | < 0.0001 |
| ECMO duration (hr), median (IQR) | 122 (70–233) | 162 (88–272) | 0.0006 | 120 (70–209) | 156 (82–267) | 0.005 |
| Mortality (% yes) | | | | | | |
| At ECMO decannulation | 66 (20.4) | 155 (31.0) | 0.0008 | 31 (15.0) | 190 (31.0) | < 0.0001 |
| By hospital discharge | 107 (33.1) | 257 (51.4) | < 0.0001 | 52 (25.1) | 311 (50.7) | < 0.0001 |
| RST performed (%) | | | < 0.0001 | NA | NA | NA |
| Yes | 114 (28.4) | 287 (71.6) | | NA | NA | |

(*Continued*)

**TABLE 2. (*Continued*). Demographic Data for Patients by Presence of Acute Kidney Injury**

| Variable | No-AKI$^{SCr}$ ($n = 323$) | AKI$^{SCr}$ ($n = 502$) | $p$ | No-AKI$^{SCr + RST}$ ($n = 207$) | AKI$^{SCr + RST}$ ($n = 615$) | $p$ |
|---|---|---|---|---|---|---|
| No | 207 (49.2) | 214 (50.8) | | NA | NA | |
| RST mode (%) | | | < 0.0001 | | | NA |
| Continuous renal replacement therapy | 21 (22.3) | 73 (77.7) | | 0 (0) | 94 (15.4) | |
| Inline hemodiafilter | 89 (30.4) | 204 (69.6) | | 0 (0) | 293 (48.1) | |
| Intermittent hemodialysis | 2 (66.7) | 1 (33.3) | | 0 (0) | 3 (0.5) | |
| Peritoneal dialysis | 1 (20.0) | 4 (80.0) | | 0 (0) | 5 (0.8) | |
| None | 207 (49.2) | 214 (50.8) | | 207 (100) | 214 (35.1) | |

AKI = acute kidney injury, ECMO = extracorporeal membrane oxygenation, IQR = interquartile range, NA = not applicable, RST = renal support therapy, SCr = serum creatinine.

Chi-square test/Fisher exact test is used to test for difference in categoric variables between groups. Wilcoxon signed rank test used to test for difference in continuous variables between groups.

**TABLE 3. Proportions of Acute Kidney Injury by Stage and Extracorporeal Membrane Oxygenation Support and Mode Types in the Pediatric Cohort**

| Variable | Examined, *n* | Stage 0 *n* (%) | Stage 1 *n* (%) | Stage 2 *n* (%) | Stage 3 *n* (%) |
|---|---|---|---|---|---|
| All support types ($n = 330$) | | | | | |
| Pre-ECMO (at initiation) | | | | | |
| AKI$^{SCr}$ | 314 | 152 (48.4) | 55 (17.5) | 58 (18.5) | 49 (15.6) |
| AKI$^{SCr + RST}$ | 310 | 109 (35.2) | 38 (12.3) | 37 (11.9) | 126 (40.7) |
| On-ECMO (≤ 48 hr) | | | | | |
| AKI$^{SCr}$ | 312 | 129 (41.4) | 53 (17.0) | 72 (23.1) | 58 (18.6) |
| AKI$^{SCr + RST}$ | 309 | 64 (20.7) | 23 (7.4) | 30 (9.7) | 192 (62.1) |
| On-ECMO (> 48 hr) | | | | | |
| AKI$^{SCr}$ | 248 | 83 (33.5) | 46 (18.6) | 56 (22.6) | 63 (25.4) |
| AKI$^{SCr + RST}$ | 245 | 31 (12.7) | 20 (8.2) | 18 (7.4) | 176 (71.8) |
| Pulmonary ($n = 162$) | | | | | |
| Pre-ECMO (at initiation) | | | | | |
| AKI$^{SCr}$ | 159 | 98 (61.6) | 25 (15.7) | 21 (13.2) | 15 (9.4) |
| AKI$^{SCr + RST}$ | 156 | 71 (45.5) | 13 (8.3) | 11 (7.1) | 61 (39.1) |
| On-ECMO (≤ 48 hr) | | | | | |
| AKI$^{SCr}$ | 153 | 78 (51.0) | 23 (15.0) | 30 (19.6) | 22 (14.4) |
| AKI$^{SCr + RST}$ | 151 | 37 (24.5) | 7 (4.6) | 11 (7.3) | 96 (63.6) |
| On-ECMO (> 48 hr) | | | | | |
| AKI$^{SCr}$ | 135 | 48 (35.6) | 21 (15.6) | 30 (22.2) | 36 (26.7) |
| AKI$^{SCr + RST}$ | 133 | 18 (13.5) | 10 (7.5) | 7 (5.3) | 98 (73.7) |

(*Continued*)

**TABLE 3. (*Continued*). Proportions of Acute Kidney Injury by Stage and Extracorporeal Membrane Oxygenation Support and Mode Types in the Pediatric Cohort**

| Variable | Examined, *n* | Stage 0 *n* (%) | Stage 1 *n* (%) | Stage 2 *n* (%) | Stage 3 *n* (%) |
|---|---|---|---|---|---|
| Cardiac ($n = 94$) | | | | | |
| Pre-ECMO (at initiation) | | | | | |
| $AKI^{SCr}$ | 88 | 32 (36.4) | 18 (20.5) | 22 (25.0) | 16 (18.2) |
| $AKI^{SCr + RST}$ | 88 | 23 (26.1) | 16 (18.2) | 16 (18.2) | 33 (37.5) |
| On-ECMO (≤ 48 hr) | | | | | |
| $AKI^{SCr}$ | 92 | 30 (32.6) | 21 (22.8) | 23 (25.0) | 18 (19.6) |
| $AKI^{SCr + RST}$ | 92 | 15 (16.3) | 11 (12.0) | 11 (12.0) | 55 (59.8) |
| On-ECMO (> 48 hr) | | | | | |
| $AKI^{SCr}$ | 71 | 18 (25.4) | 22 (31.0) | 13 (18.3) | 18 (25.4) |
| $AKI^{SCr + RST}$ | 71 | 7 (9.9) | 9 (12.7) | 6 (8.5) | 49 (69.0) |
| Extracorporeal cardiopulmonary resuscitation ($n = 74$) | | | | | |
| Pre-ECMO (at initiation) | | | | | |
| $AKI^{SCr}$ | 67 | 22 (32.8) | 12 (17.9) | 15 (22.4) | 18 (26.9) |
| $AKI^{SCr + RST}$ | 66 | 15 (22.7) | 9 (13.6) | 10 (15.2) | 32 (48.5) |
| On-ECMO (≤ 48 hr) | | | | | |
| $AKI^{SCr}$ | 67 | 21 (31.3) | 9 (13.4) | 19 (28.4) | 18 (26.9) |
| $AKI^{SCr + RST}$ | 66 | 12 (18.2) | 5 (7.6) | 8 (12.1) | 41 (62.1) |
| On-ECMO (> 48 hr) | | | | | |
| $AKI^{SCr}$ | 42 | 17 (40.5) | 3 (7.1) | 13 (31.0) | 9 (21.4) |
| $AKI^{SCr + RST}$ | 41 | 6 (14.6) | 1 (2.4) | 5 (12.2) | 29 (70.7) |
| Mode type, overall ($n = 330$) | | | | | |
| Pre-ECMO (at initiation) | | | | | |
| $AKI^{SCr}$ | 314 | 152 (48.4) | 55 (17.5) | 58 (18.5) | 49 (15.6) |
| $AKI^{SCr + RST}$ | 310 | 109 (35.2) | 38 (12.3) | 37 (11.9) | 126 (40.7) |
| On-ECMO (≤ 48 hr) | | | | | |
| $AKI^{SCr}$ | 312 | 129 (41.4) | 53 (17.0) | 72 (23.1) | 58 (18.6) |
| $AKI^{SCr + RST}$ | 309 | 64 (20.7) | 23 (7.4) | 30 (9.7) | 192 (62.1) |
| On-ECMO (> 48 hr) | | | | | |
| $AKI^{SCr}$ | 248 | 83 (33.5) | 46 (18.6) | 56 (22.6) | 63 (25.4) |
| $AKI^{SCr + RST}$ | 245 | 31 (12.7) | 20 (8.2) | 18 (7.4) | 176 (71.8) |
| Venoarterial ($n = 239$) | | | | | |
| Pre-ECMO (at initiation) | | | | | |
| $AKI^{SCr}$ | 225 | 94 (41.8) | 43 (19.1) | 47 (20.9) | 41 (18.2) |
| $AKI^{SCr + RST}$ | 222 | 69 (31.1) | 32 (14.4) | 31 (14) | 90 (40.5) |
| On-ECMO (≤ 48 hr) | | | | | |
| $AKI^{SCr}$ | 226 | 83 (36.7) | 44 (19.5) | 54 (23.9) | 45 (19.9) |
| $AKI^{SCr + RST}$ | 224 | 45 (20.1) | 21 (9.4) | 25 (11.2) | 133 (59.4) |
| On-ECMO (> 48 hr) | | | | | |
| $AKI^{SCr}$ | 170 | 55 (32.4) | 35 (20.6) | 34 (20.0) | 46 (27.1) |

(*Continued*)

**TABLE 3. (*Continued*). Proportions of Acute Kidney Injury by Stage and Extracorporeal Membrane Oxygenation Support and Mode Types in the Pediatric Cohort**

| Variable | Examined, *n* | Stage 0 *n* (%) | Stage 1 *n* (%) | Stage 2 *n* (%) | Stage 3 *n* (%) |
|---|---|---|---|---|---|
| $AKI^{SCr + RST}$ | 168 | 23 (13.7) | 14 (8.3) | 13 (7.7) | 118 (70.2) |
| Venovenous ($n = 83$) | | | | | |
| Pre-ECMO (at initiation) | | | | | |
| $AKI^{SCr}$ | 81 | 53 (65.4) | 11 (13.6) | 9 (11.1) | 8 (9.9) |
| $AKI^{SCr + RST}$ | 81 | 36 (44.4) | 6 (7.4) | 6 (7.4) | 33 (40.7) |
| On-ECMO (≤ 48 hr) | | | | | |
| $AKI^{SCr}$ | 78 | 41 (52.6) | 9 (11.5) | 15 (19.2) | 13 (16.7) |
| $AKI^{SCr + RST}$ | 78 | 17 (21.8) | 2 (2.6) | 5 (6.4) | 54 (69.2) |
| On-ECMO (> 48 hr) | | | | | |
| $AKI^{SCr}$ | 70 | 24 (34.3) | 9 (12.9) | 21 (30) | 16 (22.9) |
| $AKI^{SCr + RST}$ | 70 | 7 (10.0) | 5 (7.1) | 5 (7.1) | 53 (75.7) |
| Other modes ($n = 8$) | | | | | |
| Pre-ECMO (at initiation) | | | | | |
| $AKI^{SCr}$ | 8 | 5 (62.5) | 1 (12.5) | 2 (25) | 0 (0) |
| $AKI^{SCr + RST}$ | 7 | 4 (57.1) | 0 (0) | 0 (0) | 3 (42.9) |
| On-ECMO (≤ 48 hr) | | | | | |
| $AKI^{SCr}$ | 8 | 5 (62.5) | 0 (0) | 3 (37.5) | 0 (0) |
| $AKI^{SCr + RST}$ | 7 | 2 (28.6) | 0 (0) | 0 (0) | 5 (71.4) |
| On-ECMO (> 48 hr) | | | | | |
| $AKI^{SCr}$ | 8 | 4 (50.0) | 2 (25.0) | 1 (12.5) | 1 (12.5) |
| $AKI^{SCr + RST}$ | 7 | 1 (14.3) | 1 (14.3) | 0 (0) | 5 (71.4) |

AKI = acute kidney injury, ECMO = extracorporeal membrane oxygenation, RST = renal support therapy, SCr = serum creatinine.

with a longer duration of ECMO and increased mortality both at ECMO decannulation and by hospital discharge.

The evolution of consensus criteria for the clinical definition of AKI has affected reported incidence in many pediatric scenarios. The previously used "one size fits all" threshold creatinine level definition does not account for age-related variables, nor the prior organ function of an individual patient. In prior data collection by ELSO, AKI was identified as a SCr 1.5 mg/dL or the need for RST. For the pediatric and neonatal population, this definition underestimates AKI, as significant injury may occur and the SCr remain below the threshold of 1.5 mg/dL. The 2015 ELSO International Summary reports an incidence of 1.3–11% in using SCr, and 21–43% by the need for RST (27). In the current study, the KDIGO $AKI^{SCr}$ definition identified 60% of the cohort as having renal dysfunction and the addition of RST to the definition increased the incidence to 74%. AKI severity was significant, stage 2–3 in 86% of cases for the entire cohort and 91% of nonneonatal pediatric cases identified by both definitions across the three time periods studied.

The use of RST as a defining condition of AKI in the KDIGO criteria must be tempered with the knowledge that it is a physician-derived variable rather than patient-derived variable, and there was no standard indication across centers to trigger initiation of therapy. As a result, we systematically evaluated the contribution of RST to the incidence and outcomes by evaluating the incidence of AKI with and without RST as part of the stage 3 definition. A number of patients previously classified as stage 0 moved to stage 3 with the addition of RST to the definition, and the incidence of AKI increased from 60% to 74%, with no appreciable impact on outcomes. This may be reflective of differences in practice patterns about RST utilization in children on ECMO previously reported by our group based on survey data and will be the subject of future studies (37). RST was noted to have an effect on both duration of ECMO and survival in unadjusted analysis, but when added to the multivariable model for the effect of AKI, the results were similar to the model without RST. Further study will be required to understand the complex effect of RST on outcomes.

**TABLE 4. Univariate Analysis Examining Study Variables in Relation to Extracorporeal Membrane Oxygenation Duration (Hours)**

| Variable | Median (95% CI)¶ | *p* |
|---|---|---|
| $AKI^{SCr}$ | | 0.006 |
| AKI absent | 115.4 (103.1–129.2) | |
| AKI present | 141.5 (129.3 – 154.9) | |
| $AKI^{SCr + RST}$ | | 0.01 |
| AKI absent | 111.3 (96.6–128.2) | |
| AKI present | 137.8 (126.9–149.6) | |
| Age | | 0.04 |
| Neonatal | 135.0 (122.7–148.4) | |
| Pediatric | 115.6 (102.8–130.0) | |
| Patient complications | | 0.05 |
| Yes | 130.2 (120.4–140.9) | |
| No | 103.4 (82.9–129.0) | |
| Extracorporeal membrane oxygenation mode | | 0.10 |
| Venovenous | 141.2 (122.1–163.4) | |
| Venoarterial | 121.4 (111.4–132.4) | |
| other | 194.1 (98.9–380.7) | |
| Center | | < 0.0001 |
| A | 120.0 (104.3–138.1) | |
| B | 135.3 (108.9–168.1) | |
| C | 265.4 (217.8–323.5) | |
| D | 88.3 (75.9–102.8) | |
| E | 124.2 (108.4–142.4) | |
| F | 114.8 (66.4–198.4) | |
| RST | | < 0.0001 |
| Yes | 158.4 (142.8–175.8) | |
| No | 103.9 (93.9–114.9) | |
| | **Log β-estimate ± SE** | |
| pH | 0.208 ± 0.195 | 0.29 |

AKI = acute kidney injury, RST = renal support therapy, SCr = serum creatinine. Median is based on back transforming the least square means and 95% CI.

Limited prior data has been published beyond case reports on the timing of AKI during ECMO. Early neonatal respiratory studies identified an initial period of low urine output and fluid changes, but no data are collected in the ELSO registry to identify the timing of AKI (38). In the current study, AKI developed early in the course of ECMO, with 51–64% of AKI present at ECMO initiation and 86–93% of all cases of AKI identified by 48 hours. These data suggest that AKI risk factors are likely present prior to initiation of ECMO, rather than exposure to extracorporeal therapy. Pre-ECMO severity of illness measures (pH and need for vasoactive agents) used in this study are convenience surrogate measures, but despite this limitation were not associated with the risk for AKI to allow for identification of specific risk variables. Some authors have suggested that the need for cardiac mechanical support and nonpulsatile flow may be associated with the development of AKI (39), yet reduced urine output and positive fluid balance have also been reported in the venovenous ECMO population, suggesting lack of pulsatility is not the only variable associated with AKI on ECMO (40).

In the current study, the presence of AKI was associated with a significantly increased duration of ECMO and reduced survival to hospital discharge after controlling for patient and support variables previously associated with these outcomes. This finding is consistent with previous reports in other critically ill pediatric populations (9, 10). AKI is associated with increasing severity of illness in most critically ill populations, yet it is unknown if its presence in the ECMO population is a marker of severity of illness or a driver of mortality. Prior studies have suggested that return to pre-ECMO dry weight is associated with separation from support in the neonatal population (12, 14, 38), hence renal dysfunction and subsequent fluid overload may be a direct contributor to the increase in duration of ECMO support seen in this study. Regardless of the etiology, the finding that AKI is associated with a longer ECMO course and increased mortality risk are important both for clinical practice as well as further study.

This study has limitations predominantly related to the dataset used for analysis. The retrospective study design limits its findings to association rather than causality. Data were not collected for the calculation of previously validated severity of illness adjustments for outcomes. The neonatal cohort is problematic in the definition of AKI due to the natural history of SCr in the immediate birth period. This known limitation in defining neonatal AKI likely leads to an imprecise identification of AKI in neonates. The adjudication of neonatal AKI requires identification of the baseline SCr, and utilization of the convalescent lowest SCr may potentially underestimate AKI if this value were higher than published norms by age. This study was undertaken across six separate ECMO centers likely potentially with patients from varied socioeconomic and ethnic backgrounds with no protocolized indication for ECMO or RST support, which will potentially affect outcomes. Although general ECMO and RST practices are similar among these centers, there was no protocol or equipment standardization leading to the potential for the introduction of bias into the study. Finally, the study centers may represent a practice bias toward the application of RST that would potentially affect the incidence of $AKI^{SCr + RST}$, but should not bias the incidence of AKI by SCr measures only.

**TABLE 5. Univariate Analysis Examining Study Variables in Relation to Mortality**

| Variable | Mortality at ECMO Decannulation | | Mortality by Hospital Discharge | |
|---|---|---|---|---|
| | OR (95% CI) | *p* | OR (95% CI) | *p* |
| $AKI^{SCr}$ | | | | |
| AKI absent | 1 | | 1 | |
| AKI present | 1.75 (1.26–2.43) | 0.0009 | 2.14 (1.60–2.86) | < 0.0001 |
| $AKI^{SCr + RST}$ | | | | |
| AKI absent | 1 | | 1 | |
| AKI present | 2.55 (1.68–3.88) | < 0.0001 | 3.07 (2.16–4.36) | < 0.0001 |
| Age | | | | |
| Neonatal | 1 | | | |
| Pediatric | 1.10 (0.81–1.50) | 0.54 | 0.80 (0.60–1.06) | 0.12 |
| Patient complications | | | | |
| No | 1 | | | |
| Yes | 5.16 (2.35–11.33) | < 0.0001 | 6.31 (3.38–11.76) | < 0.0001 |
| ECMO mode | | | | |
| Venoarterial | 1 | | 1 | |
| Venovenous | 0.22 (0.14–0.35) | | 0.21 (0.15–0.31) | |
| other | 0.50 (0.11–2.38) | < 0.0001 | 0.22 (0.05–1.03) | < 0.0001 |
| Center | | | | |
| A | 1.65 (1.06–2.57) | | 0.96 (0.66–1.41) | |
| B | 1.98 (1.14–3.43) | | 2.27 (1.37–3.74) | |
| C | 1.18 (0.67–2.06) | | 0.91 (0.57–1.47) | |
| D | 1.91 (1.22–3.0) | | 1.81 (1.22–2.68) | |
| E | 1 | | 1 | |
| F | 3.02 (1.0–9.13) | 0.02 | 3.92 (1.19–12.88) | < 0.0001 |
| RST | | | | |
| No | 1 | | 1 | |
| Yes | 2.21 (1.61–3.02) | < 0.0001 | 2.79 (2.10–3.71) | < 0.0001 |
| pH | 0.14 (0.06–0.34) | < 0.0001 | 0.29 (0.13–0.61) | 0.001 |

AKI = acute kidney injury, ECMO = extracorporeal membrane oxygenation, OR = odds ratio, RST = renal support therapy, SCr = serum creatinine.

## CONCLUSIONS

Utilizing the KDIGO AKI definitions, we found a pediatric AKI incidence during ECMO higher than reported to date that allows for a more precise baseline understanding required to design intervention trials. The increase in reported incidence is valuable to the clinician as AKI onset is associated with adverse outcomes including longer duration of ECMO and reduced survival to hospital discharge. AKI occurs early in the course of ECMO, with a majority of cases identified at ECMO initiation and 86–93% of AKI acquired by 48 hours of support. Additional studies should attempt to elucidate the potentially modifiable factors associated with the development of AKI both before and during ECMO. Further studies in this cohort will evaluate the contribution of fluid overload to outcomes and the practices around the modality and timing of RST initiation and its effect on outcomes.

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**TABLE 6. Multivariable Analysis Examining Association Between Acute Kidney Injury and outcomes**

| Variable | $AKI^{SCr}$ | *p* | $AKI^{SCr + Renal\ Support\ Therapy}$ | *p* |
|---|---|---|---|---|
| Model 1 | | | | |
| Duration of ECMO (hr), median (95% CI)[a] | | | | |
| AKI absent | 110.0 (85.1–142.3) | < 0.0001 | 98.5 (75.3–128.9) | < 0.0001 |
| AKI present | 152.2 (118.3–195.9) | | 152.8 (119.1–196.2) | |
| Model 2 | | | | |
| Duration of ECMO (hours), median (95% CI)[a] | | | | |
| AKI absent | 120.7 (93.9–155.0) | 0.01 | NA | NA |
| AKI present | 149.2 (116.9–190.5) | | | |
| Model 1 | | | | |
| Mortality at ECMO decannulation, OR (CI) | | | | |
| AKI absent | 1 | | 1 | |
| AKI present | 1.19 (0.80–1.77) | 0.40 | 1.92 (1.15–3.23) | 0.01 |
| Model 2 | | | | |
| Mortality at ECMO decannulation, OR (CI) | | | | |
| AKI absent | 1 | | NA | NA |
| AKI present | 1.04 (0.69–1.56) | 0.86 | | |
| Model 1 | | | | |
| Mortality by hospital discharge, OR (CI) | | | | |
| AKI absent | 1 | | 1 | |
| AKI present | 1.77 (1.22–2.55) | 0.002 | 2.50 (1.61–3.90) | < 0.0001 |
| Model 2 | | | | |
| Mortality by hospital discharge, OR (CI) | | | | |
| AKI absent | 1 | | NA | NA |
| AKI present | 1.52 (1.04–2.21) | 0.03 | | |

AKI = acute kidney injury, ECMO = extracorporeal membrane oxygenation, NA = not applicable, OR = odds ratio, SCr = serum creatinine.
[a]Median is based on back transforming Least Square means and 95% CI values to the original scale.
Model 1: adjusted for age, center, mode, complications, and pH. Model 2: in addition to model 1, further adjusted for renal support therapy.

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