Fluid Overload and Mortality in Patients with Severe Acute Kidney Injury and Extracorporeal Membrane Oxygenation

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Abstract
Background Volume overload is increasingly being understood as an independent risk factor for increased mortality in the setting of AKI and critical illness, but little is known about its effect in the setting of extracorporeal membrane oxygenation (ECMO). We sought to evaluate the incidence of AKI and volume overload and their effect on all-cause mortality in adults after ECMO cannulation.

Methods We identified all adult patients who underwent ECMO cannulation at the University of Chicago between January 2015 and March 2017. We evaluated the incidence of KDIGO-defined AKI, RRT, and volume overload. Volume overload was defined as achieving a positive fluid balance of 10% above admission weight over the first 72 hours after ECMO cannulation. The primary outcome collected was 90 day all-cause mortality. Secondary outcomes included 30-day mortality, duration of ECMO and RRT therapy, length of stay, and dialysis independence at 90 days.

Results There were 98 eligible patients, 83 of whom developed AKI (85%); 48 (49%) required RRT and 19 (19%) developed volume overload at 72 hours. Patients with volume overload had increased risk of death at 90 days compared with those without volume overload (HR, 2.3; 95% CI, 1.3 to 4.2; P = 0.004). Patients with AKI-D had increased risk of death at 90 days compared with those without AKI-D (HR, 2.2; 95% CI, 1.3 to 3.8; P = 0.004). Volume overload remained an independent predictor of 90-day mortality when adjusting for RRT, APACHE score, weight (kg), diabetes, and heart failure (HR, 2.9; 95% CI, 1.4 to 6.0; P = 0.003).

Conclusions Volume overload and AKI are common and have significant prognostic value in patients treated with ECMO. Initiating RRT may help to control the deleterious effects of volume overload and improve mortality.

Introduction
Use of extracorporeal membrane oxygenation (ECMO) as a treatment for refractory cardiovascular and/or respiratory failure has increased substantially over the last decades (1–3). AKI is a frequent complication of critically ill patients receiving ECMO, with the mechanism of injury often being multifactorial (hemodynamic instability, inflammatory response to the membrane, related to the underlying disease process or premorbid conditions) (4–7). The incidence of AKI in the setting of ECMO is highly variable and depends on the AKI definition used and indications for ECMO; similarly, a significant number of these patients require RRT, with rates varying from 26% to 67% depending on the cohort (7–12). Kashani and colleagues have recently undertaken a meta-analysis of 41 cohort studies including >10,000 patients treated with ECMO; they demonstrated that the incidence rate of AKI remains high (pooled estimate incidence, 63%; 95% CI, 52% to 72%) but has not changed over time. Further, they demonstrated that in an adjusted analysis, patients with AKI requiring RRT (AKI-D) had an adjusted pooled odds ratio of 3.32 (95% CI, 2.21 to 4.99); I² = 82% for inpatient mortality compared with those on ECMO who did not require RRT (7).

Despite the growing literature, factors that determine increased mortality among patients with severe AKI and AKI-D on ECMO require further exploration. The effect of volume overload on general AKI populations and on pediatric patients treated with ECMO has been described (13–16). However, there are limited data on the effect of volume overload on adults requiring ECMO (17). In adult patients with AKI, volume overload (>10% increase in body weight) is associated with significantly more respiratory failure, need for mechanical ventilation, sepsis, and other adverse outcomes (18,19). Volume overload is deleterious in that it alters the volume of distribution of most drugs which can lead to inappropriate drug dosing, poor wound healing, and can even mask the presence of AKI.

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(20,21). Furthermore, after adjusting for severity of illness, patients with AKI and volume overload have significantly higher 90-day mortality (19). However, the effect of volume overload on adults requiring ECMO requiring RRT is unknown. Finally, although AKI and volume overload are both associated with adverse outcomes and are often interconnected, they may not always occur simultaneously. As such, we conducted a single-center, retrospective cohort study to examine the effect of AKI, AKI-D, and volume overload on patient outcomes in adults requiring ECMO.

Materials and Methods

The Institutional Review Board at the University of Chicago approved this study. We performed a single-center, retrospective chart review of all patients who were cannulated on venoarterial (VA) and venovenous (VV) ECMO from January 2015 to March 2017. Patients with ESKD and those who were cannulated on ECMO for <24 hours were excluded from study.

Demographic, clinical, and biochemical data were obtained from the University of Chicago electronic medical record. We collected admission data on age, race, sex, weight, and type of intensive-care unit (ICU). Clinical parameters including nephrotoxin use, presence of and Kidney Disease Improving Global Outcomes (KDIGO) stage of AKI, presence of sepsis, organ transplantation, and vasoactive use before ECMO cannulation were obtained. Baseline biochemical parameters including arterial pH, bicarbonate, and hemoglobin were obtained directly before initiation of ECMO cannulation. Baseline serum creatinine was defined as the mean outpatient value for the 6 months before the index hospital admission; when no outpatient values were available the admission creatinine was used. During the time of inpatient admission (13), cannulation that left a patient 10% above their weight at admission weight and significantly lower among patients who were volume overloaded at 72 hours (P=0.002). Patients with volume overload at 72 hours were less likely to have heart failure and diabetes (P=0.04 and P=0.06, respectively). Notably, there was no difference in critical illness scores (APACHE or sequential organ failure assessment [SOFA] score) based on volume status. All other baseline characteristics were similar between the two groups.

Supplemental Tables 1–3 demonstrate the same baseline characteristics stratified by volume overload at 7 days, RRT status, and ECMO type (VA or VV). Presence of volume overload at 7 days was associated with significantly lower admission weight and significantly higher number of vasoactives before ECMO cannulation. Receipt of RRT was more

Results

We identified 117 patients who underwent ECMO cannulation at our institution during the study period. A total of 19 patients were excluded from study, 12 patients for having received ECMO for <24 hours and seven patients for ESKD (Figure 1). In the final cohort of 98 patients, 83 (85%) developed AKI. Of those with AKI, 48 (58%) required RRT. The modality of treatment was continuous veno-venous hemodialysis (CVVHD) for all patients during the first 7 days after ECMO cannulation. Table 1 demonstrates the baseline characteristics of patients stratified by presence of volume overload at 72 hours. Admission weight was found to be significantly lower among patients who were volume overloaded at 72 hours (P=0.002). Patients with volume overload at 72 hours were less likely to have heart failure and diabetes (P=0.04 and P=0.06, respectively). Notably, there was no difference in critical illness scores (APACHE or sequential organ failure assessment [SOFA] score) based on volume status. All other baseline characteristics were similar between the two groups.

Statistical Methods

Qualitative data were recorded in a categoric fashion and quantitative covariates were measured as continuous variables. Categoric variables were reported as proportions and compared using the chi-squared test or Fisher exact test where appropriate. Continuous variables were reported as mean and SD or median and interquartile range and compared using the t test or Wilcoxon rank sum test where appropriate. The 30- and 90-day all-cause mortalities were examined using the Kaplan–Meier estimator of the survival function and survival curves were compared using the log rank test. Finally, multivariate Cox proportional hazards modeling was performed to obtain hazard ratios for 30- and 90-day mortality based on volume overload at 72 hours controlling for RRT status, Acute Physiology, Age, Chronic Health Evaluation (APACHE) score, weight (in kg), presence of diabetes mellitus, and presence of heart failure. All statistical tests were two sided and used an α level of 0.05 as a cutoff for statistical significance. Statistical analyses were performed using STATA 15 (StataCorp LP, College Station, TX).

Outcomes

Primary outcomes of 30- and 90-day all-cause mortality were observed. Secondary outcomes included volume overload after 72 hours of ECMO cannulation. Other measured outcomes included ICU length of stay, hospital length of stay, duration of ECMO cannulation, total duration of CRRT, and dialysis independence at 90 days.

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common in those with higher admission weight, coronary artery disease, and higher critical illness severity scores on the day of ECMO cannulation (as measured by APACHE and SOFA score). Patients cannulated with VA versus VV ECMO were more likely to be in the cardiac ICU, be on inotropic support, and have coronary artery disease and heart failure. On the basis of the SOFA score at ECMO cannulation, patients on VA ECMO had greater severity of illness than patients on VV ECMO, but this was not true when comparing APACHE score. We explored nephrotoxin use in the cohort and found that patients on RRT were less likely to have been exposed to angiotensin-converting enzyme inhibitors/angiotensin receptor blockers but were no more likely to be exposed to other common nephrotoxins (Supplemental Table 4).

Volume Overload and Patient Outcomes

We stratified outcomes by presence and absence of volume overload at 72 hours (Table 2). Volume overload at 72 hours was associated with significantly shorter length of stay and duration of ECMO therapy with higher 30-day and 90-day mortality rates. There were no differences in rates of AKI, RRT, or duration of CRRT comparing patients with and without volume overload. Supplemental Tables 5–7 demonstrate outcomes by volume overload at 7 days, RRT status, and ECMO type (VA or VV). Volume overload at 7 days was associated with a trend toward less dialysis independence at 90 days for patients with volume overload: one patient (6%) versus nine patients (30%) (P=0.07). A total of 15 patients who required RRT survived to 90 days and seven of those patients were dialysis independent at that time. Patients on VA ECMO had shorter total duration of ECMO therapy compared with patients on VV ECMO, but all other outcomes were the same between these groups.

For patients requiring RRT, mortality increased as volume status became increasingly positive. Patients who received RRT and were able to achieve negative fluid balance had the lowest 90-day mortality (64%; seven of 11 patients), whereas those with volume overload and RRT had a 90-day mortality of 100% (nine of nine patients) (Figure 2). Mortality did not increase with positive fluid balance in those who did not receive RRT; however, those meeting the definition of volume overload did have the highest 90-day mortality at 58% (seven of 12 patients).

There were no significant differences in achieving either negative fluid balance or volume overload between those requiring RRT and those not requiring RRT (P=0.50 and 0.23, respectively). There were no significant differences in severity of illness measured by APACHE score at the time of ECMO cannulation across volume status and RRT status (Supplemental Table 8). There was a significant difference in the mean 72-hour cumulative fluid balance in liters (mean [SD]) with those receiving RRT still being more net positive (10.1 [17.4]) compared with those without RRT (3.6 [7.9]; P=0.02). However, when looking only at fluid balance for those requiring RRT and comparing 72-hour cumulative balance in liters (mean [SD]) while receiving RRT versus not yet on RRT, those receiving RRT were less net positive (5.5 [7.5]) than those not yet on RRT (10.0 [15.9]; P=0.15) (Table 3).

Of the 48 patients requiring RRT during index hospitalization when ECMO was cannulated, 24 of them received CRRT in line with their ECMO circuit and 24 received CRRT through a central venous catheter and a circuit distinct from the ECMO machine. There were no significant differences in

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**Figure 1.** This consort diagram of our study population shows those patients excluded from the final cohort as well as those with and without volume overload at 72 hours. ECMO, extracorporeal membrane oxygenation; VA, venoarterial; VV, venovenous.
volume status based on the circuit connection. We found 29% of patients achieved negative volume status at 72 hours with CRRT in line with ECMO circuit compared with 13% for separate circuit, and 25% of patients were volume overloaded with CRRT in line with ECMO circuit compared with 13% for separate circuit ($P=0.17$). There was no difference in 90-day mortality based on the circuit connection. We found 67% 90-day mortality for patients with CRRT in line with ECMO circuit compared with 13% for separate circuit ($P=0.17$).

### Table 1. Clinical characteristics of those with and without volume overload on day 3 after ECMO cannulation

| Characteristics                | Volume Overload ($n=19$) | No Volume Overload ($n=79$) | $P$ Value |
|--------------------------------|-------------------------|-----------------------------|-----------|
| Age (years)                    | 55.2±19.8               | 54.7±12.8                   | 0.90      |
| Weight (kg)                    | 75.1±19.9               | 89.8±18.1                   | 0.002     |
| Gender                         |                         |                             | 0.60      |
| Male                           | 14 (73.7)               | 52 (65.8)                   |           |
| Female                         | 5 (26.3)                | 27 (31.2)                   |           |
| Race                           |                         |                             | 0.30      |
| Black                          | 8 (42.1)                | 36 (45.6)                   |           |
| White                          | 9 (47.4)                | 41 (51.9)                   |           |
| Other                          | 2 (10.5)                | 2 (2.5)                     |           |
| Comorbid conditions            |                         |                             |           |
| CKD                            | 7 (36.8)                | 28 (35.4)                   | 1.00      |
| Diabetes                       | 3 (15.8)                | 32 (40.5)                   | 0.06      |
| Hypertension                   | 9 (47.4)                | 50 (63.3)                   | 0.30      |
| Heart failure                  | 4 (21.1)                | 38 (48.1)                   | 0.04      |
| Coronary disease               | 11 (57.9)               | 36 (45.6)                   | 0.44      |
| CVA                            | 3 (15.8)                | 4 (5.1)                     | 0.13      |
| Cancer                         | 5 (26.3)                | 8 (10.1)                    | 0.12      |
| ICU type                       |                         |                             | 0.64      |
| Cardiac                        | 11 (57.8)               | 44 (55.6)                   |           |
| CT surgical                    | 6 (31.6)                | 26 (32.9)                   |           |
| Surgical                       | 0 (0.0)                 | 2 (2.6)                     |           |
| Medical                        | 2 (10.5)                | 7 (8.9)                     |           |
| Sepsis                         | 2 (10.5)                | 11 (13.9)                   | 1.00      |
| Mechanical ventilation         | 17 (89.5)               | 76 (92.6)                   | 0.25      |
| Vasoactive use before ECMO     | 17 (89.5)               | 63 (79.8)                   | 0.51      |
| Number of vasoactives          | 2.0±1.1                 | 1.6±1.1                     | 0.22      |
| Number of inotropes            | 1.2±0.9                 | 1.4±0.89                    | 0.49      |
| Baseline serum creatinine      | 1.1±0.46                | 1.1±0.40                    | 0.72      |
| AKI before ECMO                | 10 (52.6)               | 35 (44.3)                   | 0.61      |
| Baseline pH                    | 7.3±0.16                | 7.3±0.18                    | 0.59      |
| Baseline serum bicarbonate     | 19.2±5.5                | 20.9±6.4                    | 0.29      |
| APACHE                         | 15 (13-29)              | 19 (13-25)                  | 0.94      |
| SOFA                           | 7 (5–14)                | 8 (5–11)                    | 0.67      |
| ECMO type                      |                         |                             | 1.00      |
| VA                             | 16 (84.2)               | 64 (81.0)                   |           |
| VV                             | 3 (15.8)                | 15 (19.0)                   |           |

Data are presented as $n$ (%), mean±SD, or median (interquartile range) as appropriate. ECMO, extracorporeal membrane oxygenation; CVA, cerebral vascular accident; ICU, intensive-care unit; CT, computed tomography; APACHE, Acute Physiology, Age, Chronic Health Evaluation; SOFA, sequential organ failure assessment; VA, venaarterial; VV, venovenous.

### Table 2. Outcomes of those with and without volume overload on day 3 after ECMO cannulation

| Outcome                        | Volume Overload ($n=19$) | No Volume Overload ($n=79$) | $P$ Value |
|--------------------------------|-------------------------|-----------------------------|-----------|
| Length of ICU stay             | 11 (5–31)               | 26 (11–51)                  | 0.007     |
| Length of hospital stay        | 11 (5–31)               | 32 (16–60)                  | 0.002     |
| AKI                            | 18 (94.7)               | 65 (82.3)                   | 0.29      |
| CRRT                           | 8 (42.1)                | 40 (50.6)                   | 0.61      |
| Duration of ECMO               | 4 (3–5)                 | 7 (4–12)                    | 0.006     |
| Duration of CRRT               | 3 (1.5–10) ($n=8$)      | 10 (3.5–23.5) ($n=48$)      | 0.13      |
| Serum creatinine day 90        | 1.6 (1.2–1.9) ($n=2$)   | 1.4 (1–1.6) ($n=32$)        | 0.61      |
| Dialysis independence at 90 d | 0 (0.0) ($n=8$)         | 10 (25.0) ($n=40$)          | 0.18      |
| Mortality: 30 d                | 13 (68.4)               | 28 (35.4)                   | 0.02      |
| Mortality: 60 d                | 14 (73.7)               | 38 (48.1)                   | 0.07      |
| Mortality: 90 d                | 14 (73.7)               | 40 (50.6)                   | 0.08      |

Data are presented as $n$ (%), mean±SD, or median (interquartile range) as appropriate. ICU, intensive-care unit; CRRT, continuous RRT; ECMO, extracorporeal membrane oxygenation.
with ECMO circuit compared with 71% for separate circuit (P=0.75).

Survival Analyses
Patients with volume overload, RRT, and AKI had higher 30- and 90-day mortality compared with those without AKI. Figure 3A shows the 90-day survival curve for those with and without volume overload at 72 hours after ECMO cannulation; P=0.003 (90-day mortality 76% with volume overload versus 51% without volume overload). Figure 3B shows the 90-day survival curves for those with and without dialysis requirements; P=0.003 (90-day mortality 71% with RRT versus 42% without RRT). Figure 3C shows the 90-day survival curves for those with and without AKI; P=0.04 (90-day mortality 60% with AKI versus 40% without AKI).

Figure 4 demonstrates the survival curves stratified by RRT and volume overload status at 72 hours after ECMO cannulation. Patients with AKI-D and volume overload had the highest 90-day mortality (100%). Mortality was similar between those with AKI-D and no volume overload and those with volume overload without AKI-D. Patients without volume overload and no receipt of RRT had the highest survival with a 90-day mortality of 37%.

Univariate and Multivariate Cox Proportional Hazards Analyses
Table 4 displays the hazards of 90-day mortality in our univariate analyses and multivariate model. Volume overload at 72 hours after ECMO, AKI-D, and APACHE score were all significant predictors of 90-day mortality in univariate analysis. The relative risk of death at 90 days reported as a hazard ratio was 2.36 (95% CI, 1.32 to 4.24; P=0.003) for patients with volume overload, 2.22 (95% CI, 1.29 to 3.83; P=0.004) for patients with AKI-D, and 1.04 (95% CI, 1.02 to 1.09; P=0.001) with every one-point increase in APACHE score. Weight (in kg), presence of diabetes, and presence of heart failure were NS predictors of 90-day mortality in univariate analysis. In the multivariate analysis, the effect of volume overload on 90-day mortality was still significant after adjusting for AKI-D, APACHE score, weight, diabetes, and heart failure with a hazard ratio of 2.93 (95% CI, 1.44 to 5.96; P=0.003).

Discussion
We have demonstrated in a single-center cohort of patients receiving ECMO that patients who develop AKI-D or volume overload are at increased risk for morbidity and mortality. We analyzed the interplay between these two factors and found that, in our population, the combination of severe AKI and volume overload led to higher mortality compared with when just one of these factors was present. Before our investigation there was limited evidence investigating the effect RRT and volume overload have on ECMO patient mortality.

Schmidt et al. (17) performed a single-center, retrospective cohort study of 172 adults receiving VA and VV ECMO and demonstrated that patients who had positive fluid balance on ECMO day 3, regardless of RRT status, were more likely to experience 90-day mortality. In their adjusted analyses, day-3 fluid balance was an independent predictor of long-term mortality. Similar to our study, in their cohort, 60% (n=103) of patients received RRT in the setting of ECMO.

| Day of ECMO | Net UF on RRT (Mean (SD) in L) | Net I-O Not Yet on RRT (Mean (SD) in L) | Mean Difference in L | P Value |
|-------------|--------------------------------|----------------------------------------|----------------------|---------|
| 1           | 1.4 (3.1) (n=28)               | 7.4 (15.1) (n=20)                      | –6.0                 | 0.02    |
| 2           | 3.5 (5.6) (n=32)               | 3.5 (4.0) (n=15)                       | 0.0                  | 0.50    |
| 3           | 1.7 (3.2) (n=34)               | 1.6 (6.8) (n=11)                       | 0.1                  | 0.53    |
| 4           | 0.6 (2.1) (n=36)               | 0.4 (0.8) (n=9)                        | 0.2                  | 0.61    |
| 5           | 2.3 (4.8) (n=34)               | 2.0 (6.0) (n=8)                        | 0.3                  | 0.60    |
| 6           | 0.6 (3.6) (n=32)               | 1.6 (12.2) (n=6)                       | –1.0                 | 0.25    |
| 7           | 0.1 (2.1) (n=35)               | 0.5 (2.7) (n=4)                        | –0.4                 | 0.36    |
| Cumulative 72 hr | 5.5 (7.5) | 10.0 (15.9) | –4.5 | 0.15 |

ECMO, extracorporeal membrane oxygenation; UF, ultrafiltration; I-O, ins-outs (ins minus outs).
and receipt of CRRT did not guarantee negative fluid balance. Our data echo these findings, confirming the importance of 72-hour volume status, even after controlling for severity of illness (APACHE). Often patients on ECMO require large volumes of intravenous fluids and blood products and CRRT (or dialysis in general) does not assure the physician that the patient will achieve negative fluid balance (17). It can, however, help to achieve a less positive fluid balance, which may be an important distinction. As our data clearly show, in the setting of AKI-D, less positive fluid balance over the first 72 hours improves a patient’s chance of survival at 90 days (Figure 4). Separately, Mallory et al. (13) performed a retrospective cohort study of 424 pediatric patients receiving VV and VA ECMO and demonstrated that volume overload, based on fluid balance and admission weight (identical to our definition), was associated with longer duration of mechanical ventilation and increased morbidity and mortality. In their cohort, 44% of patients received RRT and, as with our cohort, patients remained in positive fluid balance despite ECMO and RRT support (13).

Our study demonstrates that volume overload has significant prognostic value in patients treated with ECMO. Despite our limited numbers, initiating RRT in this critically ill population may help to control the deleterious effects of volume overload. Patients who were started on RRT and never achieved a 10% increase in their overall weight survived more frequently than those who did experience a volume overloaded state. Although there is a great deal of debate in the critical care nephrology literature around the ideal timing of RRT initiation, much of this work has focused on serum creatinine-based AKI rather than fluid overload (23–25). Perhaps future efforts in patients on ECMO could be focused on the effect of RRT initiation around the avoidance of volume overload, because several studies now point to a potential clinical benefit (13,17).

One of our study’s strengths is that we used a standardized definition of volume overload (>10% fluid accumulation from baseline). As discussed above, this definition/concept of fluid overload was born out of the pediatric AKI literature where small volumes of fluid administration can have significant consequences in the youngest and smallest
Goldstein and colleagues (14) were among the first to demonstrate that in a cohort of 272 pediatric patients receiving stem cell transplants, patients who experienced AKI and developed fluid overload had significantly increased mortality. Since that time this cutoff has been investigated and validated in adult populations. In the prospective observational multicenter Program to Improve Care in Acute Renal Disease (PICARD) study, 618 adult patients with AKI in the ICU were followed to determine the link between fluid accumulation and renal recovery and mortality (19). They demonstrated an adjusted odds ratio for death associated with fluid overload at the time of AKI of 3.14 (95% CI, 1.18 to 8.33). Additionally, they demonstrated a clear increasing trend in 60-day mortality for patients receiving RRT who were unable to achieve negative balance. Those achieving negative fluid balance had a <20% mortality, whereas those with a positive fluid balance >10% had a mortality >50% (19). Our findings mirror these PICARD findings with the notable difference being a much higher mortality rate (Figure 2). Our data show a similar stepwise increase in mortality with building fluid accumulation in patients with AKI-D. Our data in those not requiring RRT are not quite as straightforward, much like the no-RRT cohort from the PICARD study, and further investigation is likely needed to determine the effect of volume overload in patients on ECMO not requiring RRT.

Our findings suggest a clinical imperative toward using strategies to mitigate volume overload early in the ECMO treatment course to improve survival outcomes. However, there is no clear evidence to suggest targeting a negative cumulative fluid balance because we were unable to demonstrate a survival advantage among those patients achieving negative fluid balance. As above, questions remain regarding the optimal timing for using strategies to mitigate volume overload as well as better understanding of competing risks such as hemodynamic instability and blood loss during treatment with ECMO.

Our study has several other strengths: it is one of the largest cohort studies to investigate the interactions between AKI, RRT, and volume overload in the setting of ECMO. Additionally, we used previously validated definitions of both volume overload (14,19) and AKI (22). Compared with previously published papers, we have a significant number of black patients in our cohort (44%)—a group that has been under-represented in the AKI and ECMO literature. However, our study suffers from all of the inherent limitations of a single-center, retrospective cohort. As such we can only
discuss associations rather than causation when attempting to link volume overload, severe AKI, and mortality. Importantly, it is our single-center electronic medical record that allowed us access to accurately calculate severity-of-illness scores, ensure excellent patient follow-up, and access to highly accurate fluid balance data. We were limited in that we lacked data specific to nonrenal ECMO complications and we were unable to account for all confounders and factors that may affect fluid balance or mortality, including insensible losses, underlying disease states, and information around interventions before arriving at the University of Chicago.

Our study is the first of its kind, identifying that using a standardized definition of volume overload is of prognostic significance in adult patients during their 72 hours of treatment with ECMO. We have also confirmed findings in the growing literature regarding the prognostic significance of volume overload and AKI-D during treatment with ECMO. Further investigation of the causal pathways and potential prevention of AKI and AKI-D are needed. Similarly, further confirmation of our findings regarding the importance of mitigating volume overload and the optimal strategies and timing of this suggested imperative are required.

Author Contributions
S. Gunning wrote the original draft; S. Gunning and J. Koyner conceptualized the study and were responsible for formal analysis; S. Gunning, J. Koyner, F. Kutuby, R. Rose, and T. Song reviewed and edited the manuscript; S. Gunning, F. Kutuby, R. Rose, T. Song, and S. Trevino were responsible for data curation; J. Koyner was responsible for investigation, methodology, and project administration; and J. Koyner and T. Song were responsible for supervision.

Disclosures
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Supplemental Material
This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.000402019/-/DSSupplemental.
Supplemental Table 1. Clinical characteristics of those with and without volume overload at day 7 after ECMO cannulation.
Supplemental Table 2. Clinical characteristics of those with and without RRT.
Supplemental Table 3. Clinical characteristics of those with VA versus VV ECMO.
Supplemental Table 4. Nephrotoxin use stratified by RRT status.
Supplemental Table 5. Outcomes of those with and without volume overload at 7 days after ECMO cannulation.
Supplemental Table 6. Outcomes of those with and without RRT.
Supplemental Table 7. Outcomes of those with VA versus VV ECMO.
Supplemental Table 8. APACHE scores by volume and RRT status.

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Supplemental Table 8 - APACHE scores by Volume and RRT Status
|                                | Volume Overload (n=32) | No Volume Overload (n=66) | p-value |
|--------------------------------|------------------------|---------------------------|---------|
| Age                            | 55.3 ± 16.0            | 54.6 ± 13.6               | 0.82    |
| Weight (kg)                    | 80.9 ± 22.2            | 89.8 ± 17.1               | 0.03    |
| Gender                         |                        |                           | 0.65    |
| Male                           | 23 (71.9)              | 43 (65.2)                 |         |
| Female                         | 9 (28.1)               | 23 (34.8)                 |         |
| Race                           |                        |                           | 0.16    |
| African American               | 15 (46.9)              | 29 (43.9)                 |         |
| Caucasian                      | 14 (43.8)              | 36 (54.6)                 |         |
| Other                          | 3 (9.4)                | 1 (1.5)                   |         |
| Co-morbid conditions           |                        |                           |         |
| CKD                            | 13 (40.6)              | 22 (33.3)                 | 0.51    |
| Diabetes                       | 12 (37.5)              | 23 (34.9)                 | 0.83    |
| Hypertension                   | 17 (53.1)              | 42 (63.6)                 | 0.38    |
| Heart Failure                  | 11 (34.4)              | 31 (47.0)                 | 0.28    |
| Coronary Disease               | 19 (59.4)              | 28 (42.4)                 | 0.14    |
| CVA                            | 4 (12.5)               | 3 (4.6)                   | 0.21    |
| Cancer                         | 7 (21.9)               | 6 (9.1)                   | 0.11    |
| ICU Type                       |                        |                           | 0.82    |
| Cardiac                        | 19 (59.4)              | 36 (54.6)                 |         |
| CT Surgical                    | 10 (31.3)              | 22 (33.3)                 |         |
| Surgical                       | 1 (3.1)                | 1 (1.5)                   |         |
| Medical                        | 2 (6.2)                | 7 (10.6)                  |         |
| Sepsis                         | 3 (9.4)                | 10 (15.2)                 | 0.54    |
| Mechanical Ventilation         | 30 (93.8)              | 63 (95.5)                 | 0.66    |
| Vasoactive use prior to ECMO   | 29 (90.6)              | 51 (77.3)                 | 0.16    |
| Number of Vasoactives          | 2.1 ± 1.0              | 1.5 ± 1.1                 | 0.01    |
| Inotrope use                   | 26 (81.2)              | 52 (78.8)                 | 1.00    |
| Number of Inotropes            | 1.3 ± 0.82             | 1.3 ± 0.90                | 0.85    |
| Baseline serum Creatinine      | 1.1 ± 0.43             | 1.1 ± 0.41                | 0.52    |
| AKI Prior to ECMO              | 17 (53.1)              | 28 (42.2)                 | 0.40    |
| Baseline pH                    | 7.26 ± 0.16            | 7.29 ± 0.19               | 0.52    |
| Baseline Serum Bicarbonate     | 19.5 ± 5.4             | 21.1 ± 6.5                | 0.25    |
| APACHE                         | 18.5 (13.5, 27.5)      | 18.5 (13, 24)             | 0.66    |
| SOFA                           | 8.5 (4.5, 11.5)        | 8 (6, 11)                 | 0.85    |
| ECMO Type                      |                        |                           | 0.78    |
| VA                             | 27 (84.4)              | 53 (80.3)                 |         |
| VV                             | 5 (15.6)               | 13 (19.7)                 |         |

Data are presented as n(%), mean ± standard deviation, or median (interquartile range) as appropriate.
CKD-Chronic Kidney Disease, CVA-Cerebral Vascular Accident, ICU-Intensive Care Unit
| Supplemental Table 2-Clinical characteristics of those with and without RRT | RRT (n=48) | No RRT (n=50) | p-value |
|-----------------------------|------------|---------------|--------|
| Age                         | 54.9 ± 13.3| 54.8 ± 15.4   | 0.97   |
| Weight (kg)                 | 90.4 ± 18.4| 82.7 ± 18.6   | 0.04   |
| Gender                      |            |               | 0.77   |
| Male                        | 33 (68.75) | 33 (66.0)     |        |
| Female                      | 15 (31.25) | 17 (34.0)     |        |
| Race                        |            |               | 0.83   |
| African American            | 23 (47.9)  | 21 (42.0)     |        |
| Caucasian                   | 23 (47.9)  | 27 (54.0)     |        |
| Other                       | 2 (4.2)    | 2 (4.0)       |        |
| Co-morbid conditions        |            |               |        |
| CKD                         | 20 (41.7)  | 15 (30.0)     | 0.23   |
| Diabetes                    | 17 (35.4)  | 18 (36.0)     | 0.95   |
| Hypertension                | 30 (62.5)  | 29 (58.0)     | 0.65   |
| Heart Failure               | 19 (39.6)  | 23 (46.0)     | 0.52   |
| Coronary Disease            | 28 (58.3)  | 19 (38.0)     | 0.04   |
| CVA                         | 4 (8.3)    | 3 (6.0)       | 0.65   |
| Cancer                      | 9 (18.75)  | 4 (8.0)       | 0.12   |
| ICU Type                    |            |               | 0.25   |
| Cardiac                     | 29 (60.4)  | 26 (52)       |        |
| CT Surgical                 | 17 (35.4)  | 16 (32)       |        |
| Surgical                    | 0 (0)      | 2 (4)         |        |
| Medical                     | 2 (4.2)    | 6 (12)        | 0.94   |
| Sepsis                      | 6 (12.5)   | 6 (12.0)      |        |
| Mechanical Ventilation      | 46 (95.8)  | 47 (94.0)     | 0.68   |
| Vasoactive use prior to ECMO| 42 (87.5)  | 37 (74.0)     | 0.09   |
| Number of Vasoactives       | 2.0 ± 1.2  | 1.4 ± 1.1     | 0.01   |
| Inotrope use                | 39 (81.25) | 39 (78.0)     | 0.69   |
| Number of Inotropes         | 1.4 ± 0.9  | 1.3 ± 0.9     | 0.39   |
| Baseline serum Creatinine   | 1.13 ± 0.38| 1.06 ± 0.44   | 0.40   |
| AKI Prior to ECMO            | 29 (60.4)  | 16 (32.0)     | 0.005  |
| Baseline pH                 | 7.28 ± 0.17| 7.28 ± 0.19   | 1.00   |
| Baseline Serum Bicarbonate  | 20.0 ± 5.8 | 21.0 ± 6.6    | 0.43   |
| APACHE                      | 22 (15.75, 30.25) | 15.5 (12, 19) | 0.004  |
| SOFA                        | 10 (6, 12.25) | 7 (5, 9.75)   | 0.03   |
| ECMO Type                   |            |               | 0.34   |
| VA                          | 41 (85.4)  | 39 (78.0)     |        |
| VV                          | 7 (14.6)   | 11 (22.0)     |        |

Data are presented as n(%), mean ± standard deviation, or median (interquartile range) as appropriate. CKD-Chronic Kidney Disease, CVA-Cerebral Vascular Accident, ICU-Intensive Care Unit
### Supplemental Table 3-Clinical characteristics of those with VA versus VV ECMO

|                      | VA ECMO (n=80) | VV ECMO (n=18) | p-value |
|----------------------|----------------|----------------|---------|
| **Age**              | 55.5 ± 14.2    | 52.1 ± 15.2    | 0.36    |
| **Weight (kg)**      | 87.8 ± 19.3    | 83.1 ± 19.3    | 0.36    |
| **Gender**           |                |                | 0.16    |
| Male                 | 51 (63.75)     | 15 (83.3)      |         |
| Female               | 29 (36.25)     | 3 (16.7)       |         |
| **Race**             |                |                | 0.91    |
| African American     | 36 (45.0)      | 8 (44.4)       |         |
| Caucasian            | 41 (51.25)     | 9 (50.0)       |         |
| Other                | 3 (3.75)       | 1 (5.6)        |         |
| **Co-morbid conditions** |              |                |         |
| CKD                  | 32 (40.0)      | 3 (16.7)       | 0.10    |
| Diabetes             | 30 (37.5)      | 5 (27.8)       | 0.60    |
| Hypertension         | 51 (63.75)     | 8 (44.4)       | 0.18    |
| Heart Failure        | 40 (50.0)      | 2 (11.1)       | 0.003   |
| Coronary Disease     | 43 (53.75)     | 4 (22.2)       | 0.02    |
| CVA                  | 6 (7.5)        | 1 (5.6)        | 1.00    |
| Cancer               | 10 (12.5)      | 3 (16.7)       | 0.70    |
| **ICU Type**         |                |                | <0.001  |
| Cardiac              | 53 (66.25)     | 2 (11.1)       |         |
| CT Surgical          | 26 (32.5)      | 6 (33.3)       |         |
| Surgical             | 0 (0.0)        | 2 (11.1)       |         |
| Medical              | 1 (1.25)       | 8 (44.4)       |         |
| **Sepsis**           | 11 (13.75)     | 2 (11.1)       | 1.00    |
| **Mechanical Ventilation** | 76 (95.0)   | 17 (94.4)      | 1.00    |
| **Vasoactive use prior to ECMO** | 67 (83.75)   | 13 (72.22)     | 0.31    |
| **Number of Vasoactives** | 1.8 ± 1.1     | 1.4 ± 1.2      | 0.17    |
| **Inotrope use**     | 73 (91.25)     | 5 (27.8)       | <0.001  |
| **Number of Inotropes** | 1.5 ± 0.76    | 0.50 ± 0.86    | <0.001  |
| **Baseline serum Creatinine** | 1.1 ± 0.43   | 0.86 ± 0.23    | 0.01    |
| **AKI Prior to ECMO** | 39 (48.5)     | 6 (33.3)       | 0.30    |
| **Baseline pH**      | 7.25 ± 0.17    | 7.34 ± 0.19    | 0.10    |
| **Baseline Serum Bicarbonate** | 19.6 ± 5.6   | 25.0 ± 6.8     | 0.006   |
| **APACHE**           | 19 (13, 27)    | 16 (15, 21)    | 0.54    |
| **SOFA**             | 9 (5, 12)      | 7.5 (3, 9)     | 0.05    |

Data are presented as n(%), mean ± standard deviation, or median (interquartile range) as appropriate. CKD-Chronic Kidney Disease, CVA-Cerebral Vascular Accident, ICU-Intensive Care Unit.
| Nephrotoxin Use                | RRT (n=48) | No RRT (n=50) | p-value |
|--------------------------------|------------|---------------|---------|
| Any Nephrotoxin Use           | 39 (81.25) | 41 (82)       | 0.92    |
| ACEi/ARB                      | 1 (2.1)    | 11 (22)       | 0.003   |
| MRA                           | 4 (8.3)    | 4 (8)         | 0.95    |
| Diuretic                      | 27 (56.25) | 32 (64)       | 0.49    |
| NSAID                         | 1 (2.1)    | 5 (10)        | 0.16    |
| Aminoglycoside                | 3 (6.25)   | 7 (14)        | 0.21    |
| Amphotericin                  | 1 (2.1)    | 3 (6)         | 0.33    |
| Calcineurin Inhibitor         | 4 (8.3)    | 11 (22)       | 0.06    |
| Contrast                      | 23 (47.9)  | 20 (40)       | 0.43    |
### Supplemental Table 5 - Outcomes of those with and without Volume Overload at 7 Days after ECMO Cannulation

|                                | Volume Overload (n=32) | No Volume Overload (n=66) | p-value |
|--------------------------------|------------------------|---------------------------|---------|
| Length of ICU Stay             | 14.5 (6, 43)           | 25 (11, 47)               | 0.11    |
| Length of Hospital Stay        | 15.5 (6, 45)           | 31 (16, 60)               | 0.03    |
| AKI                            | 30 (93.75)             | 53 (80.3)                 | 0.13    |
| CRRT                           | 18 (56.3)              | 30 (45.5)                 | 0.39    |
| Duration of ECMO               | 5 (3, 6.5)             | 7 (4, 15)                 | 0.03    |
| Duration of CRRT               | 8 (4, 23)              | 9 (2, 23)                 | 0.93    |
| Serum Creatinine Day 90        | 1.6 ± 0.31             | 1.5 ± 0.80                | 0.92    |
| Dialysis independence at 90 days | 1 (5.6)               | 9 (30.0)                  | 0.07    |
| 30 day mortality              | 19 (59.4)              | 22 (33.3)                 | 0.02    |
| 60 day mortality              | 22 (68.8)              | 30 (45.5)                 | 0.03    |
| 90 day mortality              | 23 (71.9)              | 31 (47.0)                 | 0.03    |

Data are presented as n(%), mean ± standard deviation, or median (interquartile range) as appropriate.

ICU- Intensive Care Unit; n/a - Not Applicable
|                                | RRT (n=48)       | No RRT (n=50)     | p-value |
|--------------------------------|------------------|-------------------|---------|
| Length of ICU Stay             | 21 (8.5, 54)     | 23 (12, 33.75)    | 0.93    |
| Length of Hospital Stay        | 27 (10, 60)      | 31 (16, 46.75)    | 0.65    |
| Duration of ECMO               | 6.5 (4, 20.25)   | 5 (3, 9.75)       | 0.08    |
| Duration of CRRT              | 9.5 (3.25, 23)   | n/a               | n/a     |
| AKI                            |                  |                   |         |
| Serum Creatinine Day 90        | 1.5 (1.1, 1.6)   | 1.4 (1.1, 1.6)    | 0.96    |
| Negative Cumulative Fluid Balance | 17 (35.4)       | 21 (42.0)         | 0.50    |
| Volume Overload                | 19 (39.6)        | 14 (28.0)         | 0.23    |
| Dialysis independence at 90 days | 7 (14.6)         | n/a               | n/a     |
| 30 day mortality              | 27 (56.3)        | 15 (30.0)         | 0.009   |
| 60 day mortality              | 32 (66.7)        | 21 (42.0)         | 0.014   |
| 90 day mortality              | 33 (68.8)        | 21 (42.0)         | 0.002   |

Data are presented as n(%), mean ± standard deviation, or median (interquartile range) as appropriate.

ICU- Intensive Care Unit; n/a -Not Applicable
| Outcome                          | VA ECMO (n=80) | VV ECMO (n=18) | p-value |
|---------------------------------|----------------|----------------|---------|
| Length of ICU Stay              | 21 (9, 46)     | 32 (22, 55)    | 0.04    |
| Length of Hospital Stay         | 27 (10, 49)    | 39.5 (26, 65)  | 0.06    |
| AKI                             | 70 (87.5)      | 13 (72.2)      | 0.14    |
| RRT                             | 41 (51.25)     | 7 (38.9)       | 0.44    |
| Duration of ECMO                | 5 (3, 10.5)    | 10.5 (5, 22)   | 0.02    |
| Duration of CRRT                | 8 (3, 22)      | 18 (2.24)      | 0.45    |
| Serum Creatinine Day 90         | 1.4 (1, 1.6)   | 1.4 (1.1, 2.5) | 0.29    |
| Dialysis independence at 90 days| 7 (17.1)       | 3 (42.9)       | 0.15    |
| 30 day mortality                | 34 (42.5)      | 7 (38.9)       | 1.00    |
| 60 day mortality                | 43 (53.75)     | 9 (50.0)       | 0.80    |
| 90 day mortality                | 46 (57.5)      | 8 (44.4)       | 0.43    |

Data are presented as n(%), mean ± standard deviation, or median (interquartile range) as appropriate.

ICU- Intensive Care Unit; n/a - Not Applicable
Supplemental Table 8- APACHE scores by Volume and RRT Status

|                          | Net Negative fluid balance | Neither negative or Positive | Fluid Overload | P value |
|--------------------------|-----------------------------|------------------------------|----------------|---------|
| Whole Cohort regardless of RRT status | 16 (12, 21) (n=25) | 19.5 (14, 25.5) (n=48) | 18 (14, 29) (n=21) | 0.242 |
| Entire RRT Cohort (N=48) | 20 (15, 30) (n=11) | 21 (16.5, 28.5) (n=28) | 29 (27, 34) (n=9) | 0.264 |
| CRRT started Prior to ECMO (N=11) | 15 (15, 15) (n=1) | 21 (20, 27) (n=9) | 27 (27, 27) (n=1) | 0.142 |
| CRRT started After ECMO (n=37) | 20 (15, 30) (n=10) | 21 (13, 31) (n=19) | 30.5 (21, 35) (n=8) | 0.408 |
| Never on CRRT (n=50) | 13.5 (12, 19) (n=14) | 17 (13, 20) (n=20) | 15 (12.5, 18) (n=12) | 0.463 |