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Fluid Overload and Mortality in Patients with Severe Acute Kidney Injury and Extra Corporeal 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 acute kidney injury (AKI) and critical illness, but little is known about its impact in the setting of extracorporeal membrane oxygenation (ECMO). We sought to evaluate the incidence of AKI and volume overload and their impact on all-cause mortality in adults following 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, renal replacement therapy (RRT) and volume overload. Volume overload was defined as achieving a positive fluid balance of 10% above admission weight over the first 72 hours following 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%); with 48 (49%) requiring RRT and 19 (19%) developing volume overload at 72 hours. Patients with volume overload had increased risk of death at 90 days compared to those without volume overload (HR 2.3(1.3, 4.2); p=0.004). Patients with AKI-D had increased risk of death at 90 days compared to those without AKI-D (HR 2.2(1.3, 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(1.4, 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.

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] Acute kidney injury (AKI) is a frequent complication of critically ill patients receiving ECMO with the mechanism of injury often being multi-factorial (hemodynamic instability, inflammatory response to the membrane, related to the underlying disease process or pre-morbid conditions). [4-7] The incidence of AKI in the setting of ECMO is highly variable and depends on the AKI definition employed and indications for ECMO; similarly, a significant number of these patients require renal replacement therapy with rates varying from 25.5% to 67% depending on the cohort. [7-12] Kashani and colleagues have recently undertaken a meta-analysis of 41 cohort studies including more than 10,000 patients treated with ECMO; they demonstrated that the incidence rate of AKI remains high (pooled estimate incidence (95% CI) 62.8% (52.1%-72.4%) 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 (95% CI) of 3.32 (2.21-4.99); I^2=82% for inpatient mortality compared to 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 impact of volume overload on general AKI populations and on pediatric patients treated with ECMO has been described. [13-16] However, there is limited data on the impact of volume overload on adults requiring ECMO. [17] In adult patients with AKI, volume overload (greater than 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, leads to poor wound healing and can even mask the presence of AKI.[20, 21] Furthermore, after adjusting for severity of illness, patients with AKI and volume overload have significantly higher 90 day mortality. [19] However the impact of volume overload on adults requiring ECMO requiring renal replacement therapy is unknown. Finally, although AKI and volume overload are both associated with adverse outcomes and are often inter-connected, they may not always occur simultaneously. As such, we conducted a single-center retrospective cohort study to examine the impact of AKI, AKI-D, and volume overload on patient outcomes in adults requiring ECMO.

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 veno-arterial and veno-venous extracorporeal membrane oxygenation (VA and VV ECMO) from January 2015 to March 2017. Patients with end stage renal disease (ESRD) and those who were cannulated on ECMO for less than 24 hours were excluded from study.

Demographic, clinical, and biochemical data were obtained from the University of Chicago electronic medical record (EMR). We collected admission data on age, race, sex, weight, and type of ICU. Clinical parameters including nephrotoxin use, presence of and KDIGO stage of AKI, presence of sepsis, organ transplantation, and vasoactive use prior to ECMO cannulation were obtained. Baseline biochemical parameters including arterial pH, bicarbonate, and hemoglobin were obtained directly prior to initiation of ECMO therapy. Baseline serum creatinine was defined as the mean outpatient value for the 6 months prior to the index hospital admission; when no outpatient values were available the admission creatinine was utilized. During the first 7 days of ECMO cannulation, daily fluid balance (total documented inputs minus total documented outputs) was obtained. As previously described, volume overload was defined as achieving a positive fluid balance over the first 72 hours and first 7 days of ECMO cannulation that left a patient 10% above their weight at the time of inpatient admission.[13] Cumulative fluid balance at the end of the first 72 hours and first 7 days of ECMO cannulation was categorized into three groups: negative (negative cumulative fluid balance), no volume overload (positive cumulative fluid balance but not greater than 10% of admission weight), and volume overload (as described above).

Volume Overload if [(fluid balance (liters in – liters out)/weight in kilograms at hospital admission] x 100 > 10

AKI was defined using the serum creatinine and urine output definitions of the Kidney Disease Improving Global Outcomes criteria.[22] Patients who required renal replacement therapy (RRT) during their index hospitalization for ECMO cannulation were identified. Information regarding CRRT during the first 7 days of ECMO cannulation – connection in line with ECMO circuit, number of cartridge changes, and duration were also obtained. In March 2016 protocols regarding CRRT in the setting of ECMO were established to make inserting the CRRT into the ECMO circuit the standard of care. Patients with dialysis catheters prior to ECMO may have had CRRT continued via catheter or switched to the ECMO circuit depending on clinical circumstances and provider preference.

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.

Statistical Methods

Qualitative data were recorded in a categorical fashion and quantitative covariates were measured as continuous variables. Categorical variables were reported as proportions and compared using χ^2 test or Fisher's exact test where appropriate. Continuous variables were reported as mean and standard deviation or median and interquartile range and compared using Student's t-test or Wilcoxon's rank sum test where appropriate. 30 and 90 day all-cause mortality were examined using the Kaplan-Meier estimator of the survival function and survival curves 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 RRT status, APACHE score, weight (in kg), presence of diabetes mellitus, and presence of heart failure. All statistical tests were two-sided and used an alpha level 0.05 as a cut off for statistical significance. Statistical analyses were performed using STATA 15 (StataCorp LP, College Station TX, USA).

Results

We identified 117 patients who underwent ECMO cannulation at our institution during the study period. 19 patients were excluded from study, 12 patients for having received ECMO for less than 24 hours and 7 patients for ESRD (Figure 1). In the final cohort of 98 patients, 83 (84.7%) developed AKI. Of those with AKI, 48 (57.8%) required RRT. The modality of treatment was 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 (APCHE or SOFA) 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 prior to ECMO cannulation. Receipt of RRT was more 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, have coronary artery disease and heart failure. On the basis of 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 ACEi/ARB 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 – 1 patient (5.6%) versus 9 patients (30%) (p=0.07). Fifteen patients who required RRT survived to 90 days and 7 of those patients were dialysis independent at that time. Patients on VA ECMO had shorter total duration of ECMO therapy compared to patients on VV ECMO but all other outcomes were the same between these groups.

For patient's 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% (7 of 11 patients)). While those with volume overload and RRT had a 90 day mortality of 100% (9 of 9) (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% (7 of 12).

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 to 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 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 to 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 71% for separate circuit (p=0.75).

Survival Analyses

Patients with volume overload, RRT, and AKI had higher 30 and 90 day mortality compared to 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=0.0026 (90 day mortality 76% with volume overload vs 51% without volume overload). Figure 3b shows the 90 day survival curves for those with and without dialysis requirements; p=0.0029 (90 day mortality 71% with RRT vs 42% without RRT). Figure 3c shows the 90 day survival curves for those with and without AKI; p=0.0398 (90 day mortality 60% with AKI vs 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. Relative risk of death at 90 days reported as HR (95% confidence interval) was 2.36 (1.32, 4.24); p=0.003 for patients with volume overload, 2.22 (1.29, 3.83); p=0.004 for patients with AKI-D, and 1.04 (1.02, 1.09) p=0.001 with every one point increase in APACHE score. Weight (in kg), presence of diabetes, presence of heart failure were not significant predictors of 90 day mortality in univariate analysis. In the multivariate analysis, the impact of volume overload on 90 day mortality was still significant after adjusting for AKI-D, APACHE score, weight, diabetes, and heart failure with HR (95% confidence interval) 2.93 (1.44, 5.96) p=0.003.

Discussion

We have demonstrated that 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 to when just one of these factors was present. Prior to our investigation there was limited evidence investigating the impact RRT and volume overload have on ECMO patient mortality.

Schmidt and colleagues 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.[17] Similar to our study, in their cohort 60% (n=103) of patients received RRT in the setting of ECMO and receipt of CRRT did not guarantee negative fluid balance. Our data echoes these findings confirming the importance of 72 hours 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 the patient will achieve negative fluid balance.[17] It can however help to achieve less positive fluid balance, which may be an important distinction. As our data clearly shows 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 and colleagues 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. While 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 ECMO patients could be focused on the impact of RRT initiation around the avoidance of volume overload, as several studies now point to a potential clinical benefit. [13, 17]

One of our study's strengths is that we employed 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 of patients. Goldstein and colleagues were amongst the first to demonstrate that in a cohort of 272 pediatric patients receiving stem cell transplant, patients who experienced AKI and developed greater than 10% fluid overload had significantly increased mortality.[14] 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 ICU patients with AKI were followed to determine the link between fluid accumulation and renal recovery and mortality.[19] They demonstrated an adjusted odds ratio (95% CI) for death associated with fluid overload at the time of AKI of 3.14 (1.18 – 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 less than 20% mortality, while those with positive fluid balance greater than 10% had a mortality over 50%. [19] Our findings mirror these PICARD findings with the notable difference being much higher mortality rate (**Figure 2**). Our data shows a similar stepwise increase in mortality with building fluid accumulation in patients with AKI-D. Our data in those not requiring RRT is not quite as straightforward, much like the No RRT cohort from the PICARD study, and further investigation is likely needed to determine the impact of volume overload in ECMO patients not requiring RRT.

Our findings suggest a clinical imperative toward employing strategies to mitigate volume overload early in the ECMO treatment course in order to improve survival outcomes. However, there is no clear evidence to suggest targeting a negative cumulative fluid balance as we were unable to demonstrate a survival advantage amongst those patients achieving negative fluid balance. As above, questions remain regarding the optimal timing for employing 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, in that 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 to previously published papers we have a significant number of African Americans in our cohort (44%) a group that has been under represented in the

AKI and ECMO literature. However, our study suffers from all 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 this single center factor that allowed us access to accurately calculate severity of illness scores, ensure excellent patient follow-up as well as highly accurate fluid balance data given the single center electronic medical record. We were limited in that we lacked data specific to non-renal ECMO complications as well as the inability to account for all confounders and factors that may impact fluid balance or mortality, including insensible losses, underlying disease states and information around interventions prior to 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.

Disclosures

J Koyner reports grants from Nxstage Medical, personal fees from Baxter, and grants from Satellite HealthCare during the conduct of the study; grants and personal fees from Astute Medical and personal fees from Sphingotec outside the submitted work. Coauthors have nothing to disclose.

Author Contributions

S Gunning: Conceptualization; Data curation; Formal analysis; Writing - original draft; Writing - review and editing

F Kutuby: Data curation; Writing - review and editing

R Rose: Data curation; Writing - review and editing

S Trevino: Data curation

T Song: Data curation; Supervision; Writing - review and editing

J Koyner: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing - review and editing

Figure 1. Consort diagram of our study population

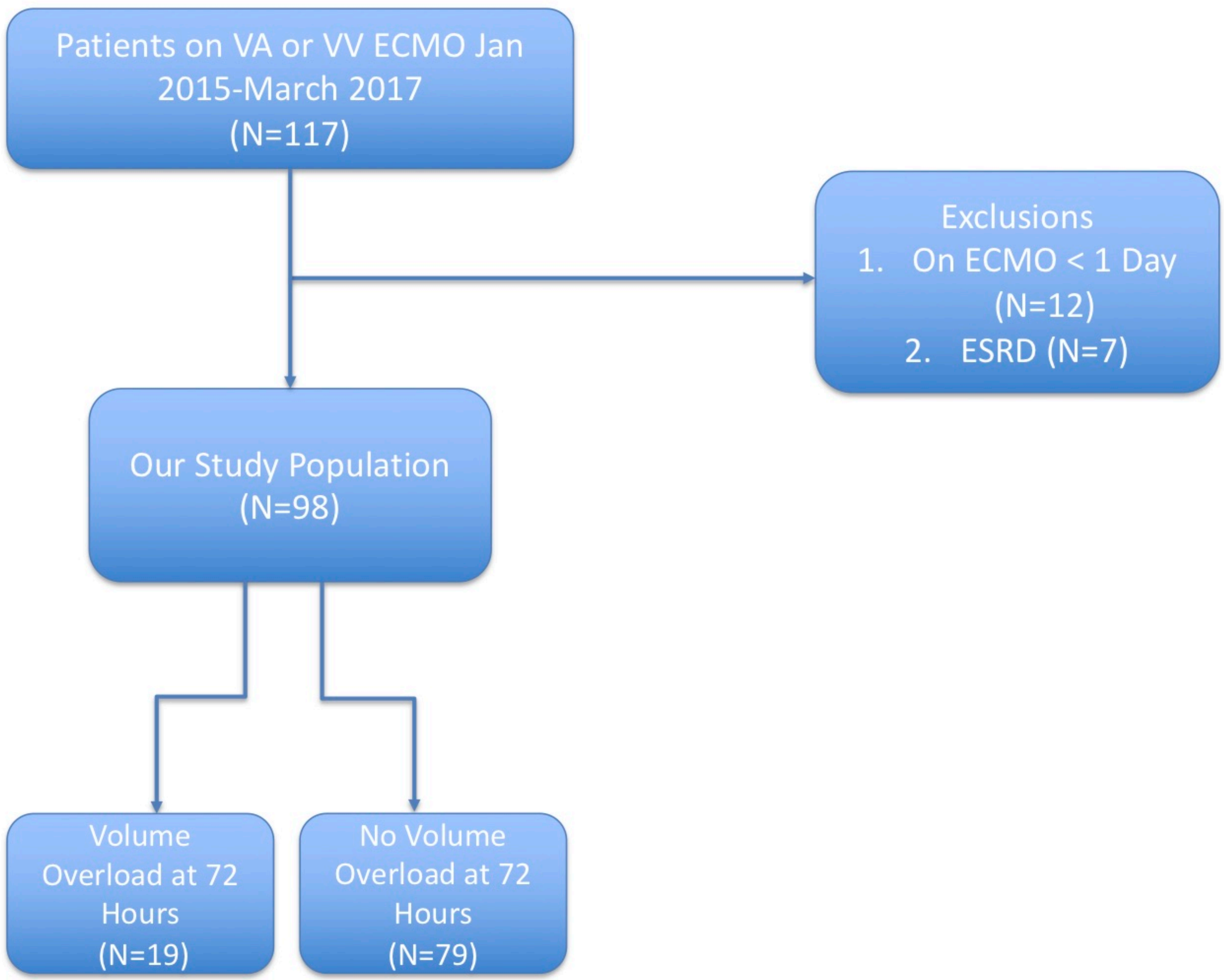

Figure 2. 90-Day Mortality in patients stratified by volume overload and dialysis status.
There were a total of 26 patients who achieved negative volume balance during the first 72 hours of ECMO. Of those, 11 were on RRT and 15 were not on RRT and 90 day mortality was 64% and 47% respectively. There were a total of 51 patients who were in positive volume balance during the first 72 hours of ECMO but did not meet the definition for volume overload. Of those, 28 were on RRT and 23 were not on RRT and 90 day mortality was 68% and 33% respectively. There were a total of 21 patients with volume overload during the first 72 hours of ECMO. Of those, 9 were on RRT and 12 were not on RRT and 90 day mortality was 100% and 58% respectively.

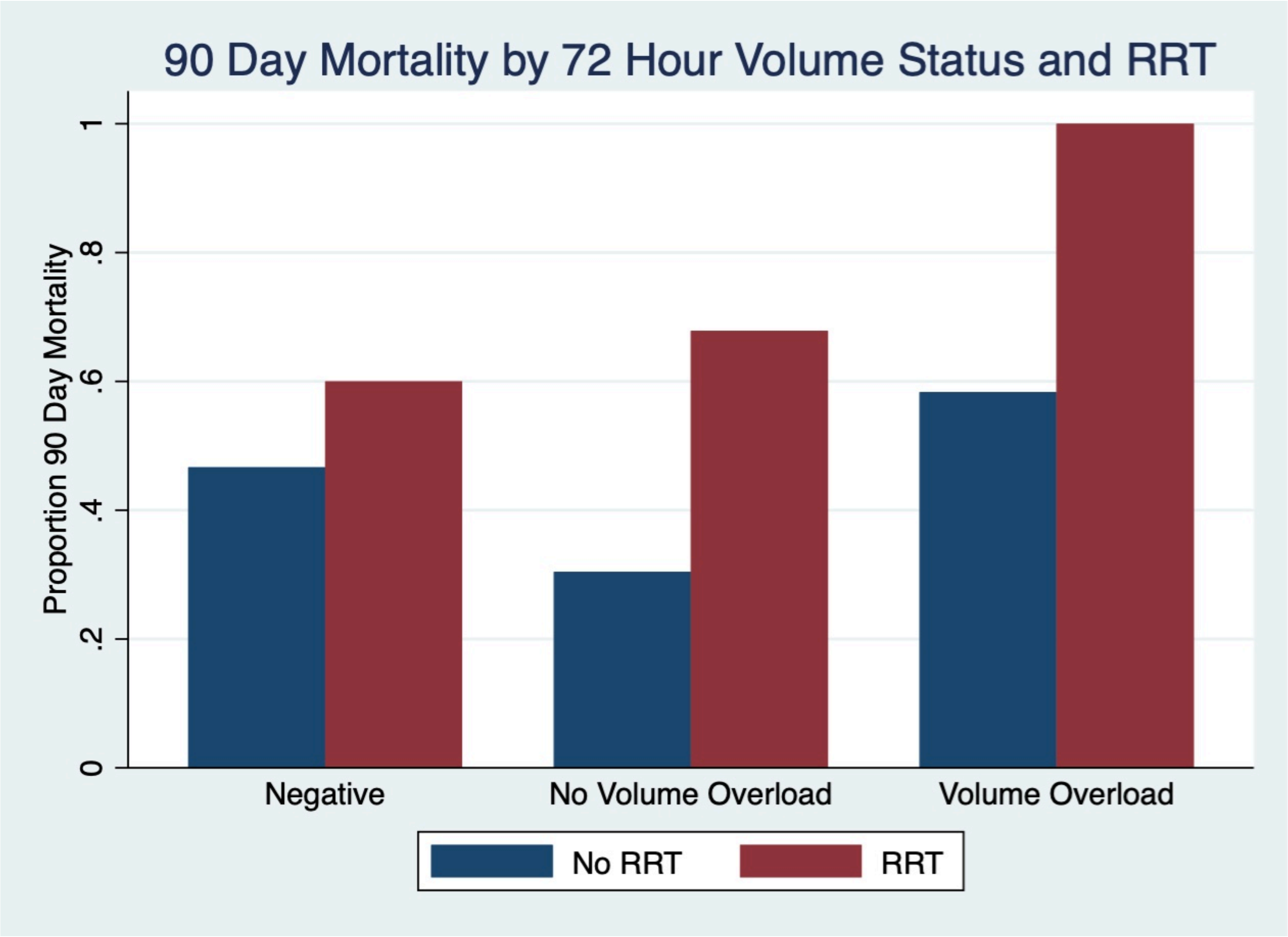

Figure 3a, b, c. Survival Curves based on Volume Overload, RRT, and AKI: 90 day survival curves for patients with and without volume overload during the first 72 hours of ECMO (p=0.0026) (a), with and without RRT (p=0.0029) (b), and without and without AKI (p=0.0398) (c). Difference between the survival curves tested employing the log rank method.

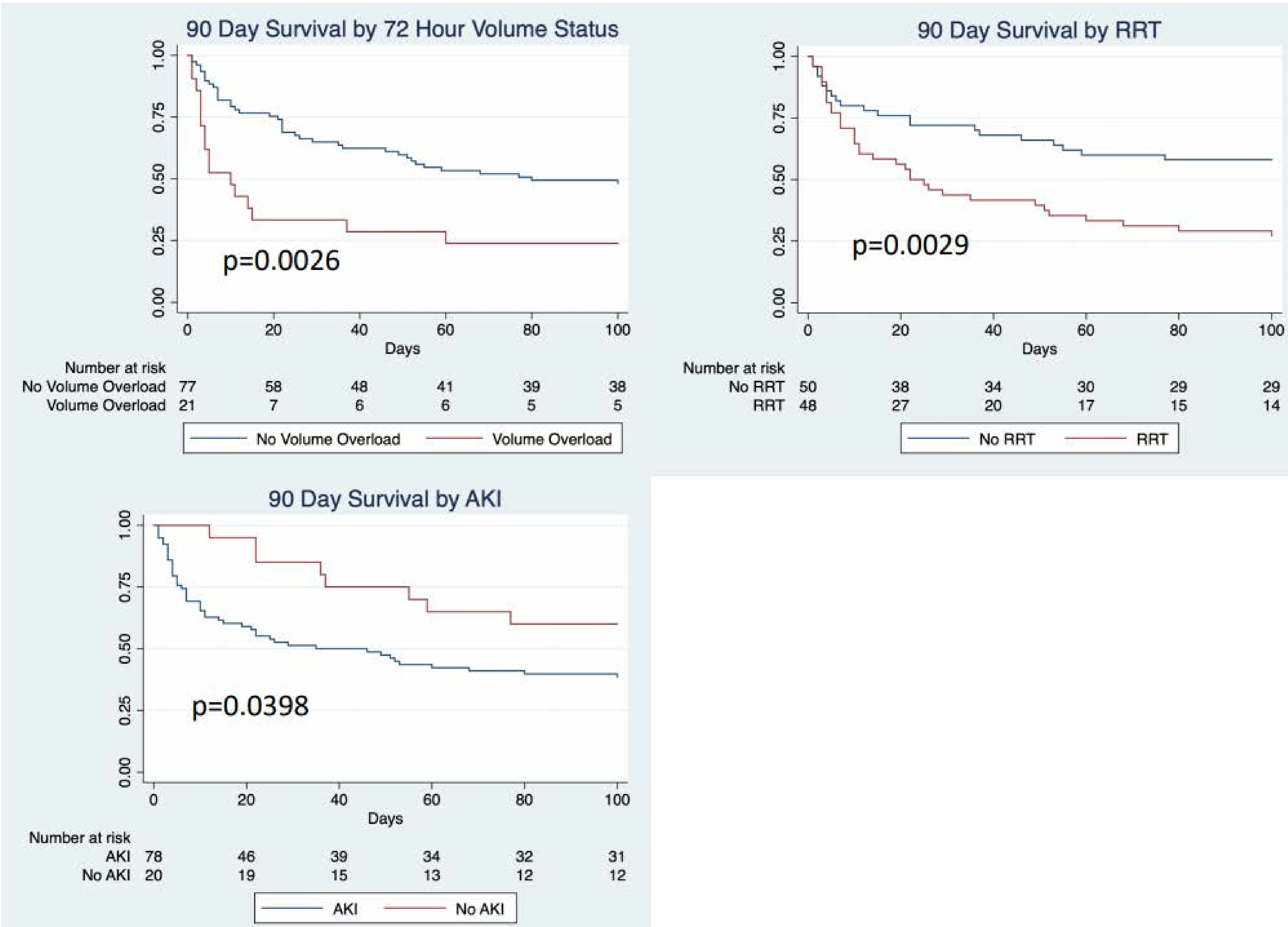

Figure 4. **Impact of Volume Overload and RRT on Survival:** The 90-day survival curve for patients stratified by volume overload at 72 hours after ECMO cannulation and RRT status are shown (p<0.001). Patients with no dialysis requiring AKI or volume overload had the lowest 90-day mortality (37%) while those with both dialysis requiring AKI and volume overload did the worst (100%). There was no difference in mortality between those with dialysis requiring AKI but no volume overload and those with volume overload but no dialysis requiring AKI (64% and 58%, respectively).

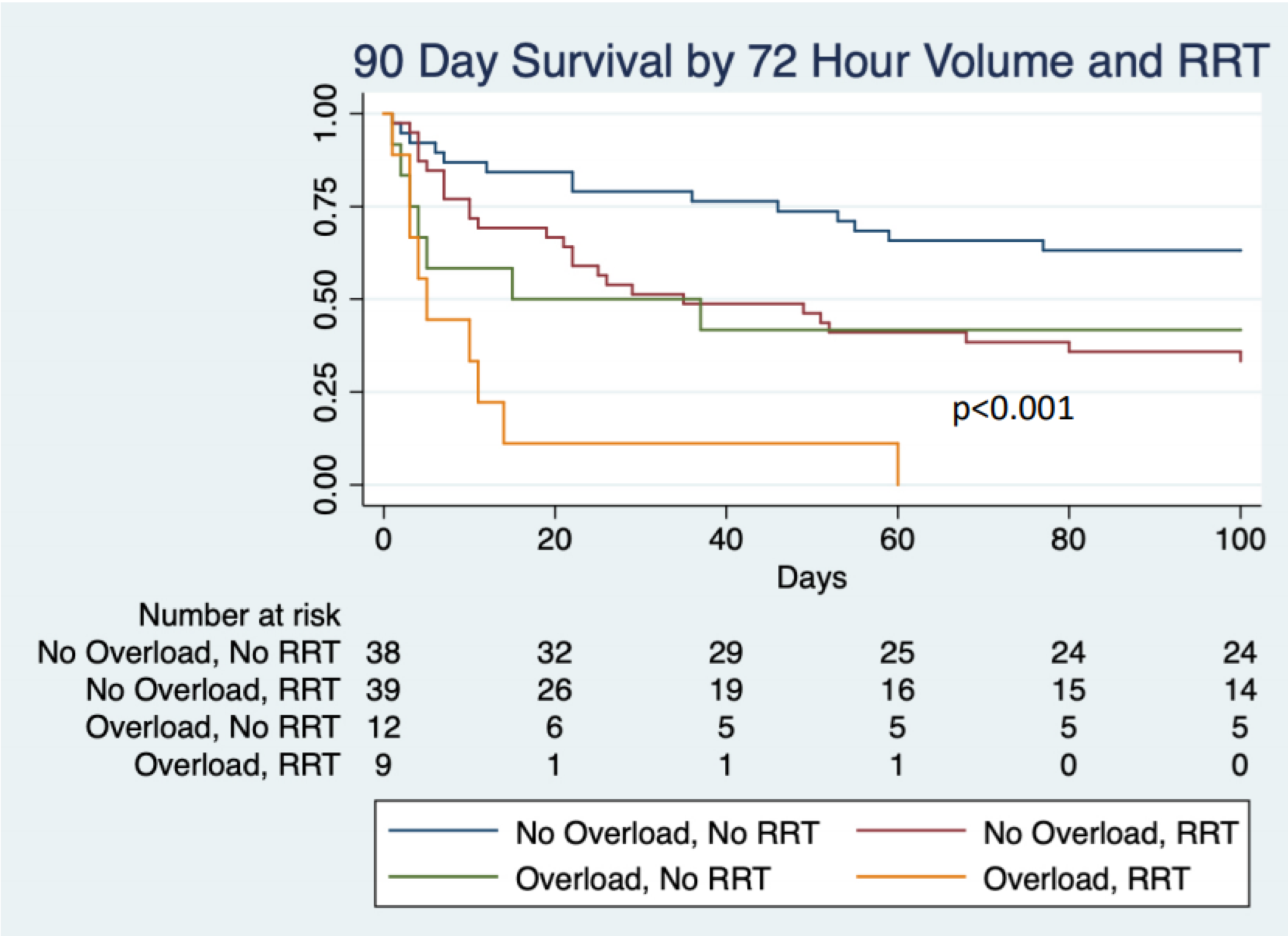

Table 1- Clinical Characteristics of those with and without volume overload on Day 3 after ECMO Cannulation

		Volume Overload (n=19)	No Volume Overload (n=79)	p-value
Age		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
	African American	8 (42.1)	36 (45.6)	
	Caucasian	9 (47.4)	41 (51.9)	
	Other	2 (10.5)	2 (2.5)	
Co-morbid 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 (96.2)	0.25
Vasoactive use prior to ECMO		17 (89.5)	63 (79.8)	0.51
Number of Vasoactives		2.0 ± 1.1	1.6 ± 1.1	0.22
Inotrope use		16 (84.2)	62 (78.5)	0.76
Number of Inotropes		1.2 ± 0.79	1.4 ± 0.89	0.49
Baseline serum Creatinine		1.1 ± 0.46	1.1 ± 0.40	0.72
AKI Prior to 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 ± standard deviation, or median (interquartile range) as appropriate.
CKD-Chronic Kidney Disease, CVA-Cerebral Vascular Accident, ICU-Intensive Care Unit

Table 2- Outcomes of those with and without volume overload on Day 3 after ECMO cannulation

	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 days	0 (0.0) (n=8)	10 (25.0) (n=40)	0.18
30 day mortality	13 (68.4)	28 (35.4)	0.02
60 day mortality	14 (73.7)	38 (48.1)	0.07
90 day mortality	14 (73.7)	40 (50.6)	0.08

Data are presented as n(%), mean ± standard deviation, or median (interquartile range) as appropriate.
ICU- Intensive Care Unit; n/a -Not Applicable

Table 3- Daily net fluid balance for patients on RRT (n=48)

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 (1.2) (n=6)	-1.0	0.25
7	0.1 (2.1) (n=33)	0.5 (2.7) (n=4)	-0.4	0.36
Cumulative 72 Hours	5.5 (7.5)	10.0 (15.9)	-4.5	0.15

Table 4- Cox Proportional Hazards Models Predicting 90 Day Mortality

Univariate Analyses		
Predictor	HR (95% Confidence Interval)	p-value
Volume Overload at 72 Hours	2.36 (1.32-4.24)	0.004
Renal Replacement Therapy (RRT)	2.22 (1.29-3.83)	0.004
APACHE	1.04 (1.02-1.07)	0.001
Weight (kg)	1.0 (0.99-1.02)	0.587
Diabetes	0.87 (0.50-1.50)	0.619
Heart Failure	0.74 (0.43-1.25)	0.260
Multivariate Model Volume Overload at 72 Hours Adjusted for RRT, APACHE, Weight Diabetes, and Heart Failure		
	2.93 (1.44-5.96)	0.003

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