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Renal Recovery in Critically Ill Adult Patients Treated With Veno-Venous or Veno-Arterial Extra Corporeal Membrane Oxygenation: A Retrospective Cohort Analysis

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Abstract

Introduction: Patients on extracorporeal membrane oxygenator (ECMO) therapy are critically ill and often develop acute kidney injury (AKI) during hospitalisation. Little is known about the association of exposure to and the effect of the type of ECMO and extent of renal recovery after AKI development. **Aim of the study**: In patients who developed AKI, renal recovery was characterised as complete, partial or dialysis-dependent at the time of hospital discharge in both the Veno-Arterial (VA) and Veno-Venous (VV) ECMO treatment groups. **Material and methods**: The study consisted of a single-centre retrospective cohort that includes all adult patients (n=125) who received ECMO treatment at a tertiary academic medical centre between 2015 to 2019. Data on demographics, type of ECMO circuit, comorbidities, exposure to nephrotoxic factors and receipt of renal replacement therapy (RRT) were collected as a part of the analysis. Acute Kidney Injury Network (AKIN) criteria were used for the diagnosis and classification of AKI. Group differences were assessed using Fisher's exact tests for categorical data and independent t-tests for continuous outcomes. **Results**: Sixty-four patients received VA ECMO, and 58 received VV ECMO. AKI developed in 58(91%) in the VA ECMO group and 51 (88%) in the VV ECMO group (p=0.77). RRT was prescribed in significantly higher numbers in the VV group 38 (75%) compared to the VA group 27 (47%) (p=0.0035). At the time of discharge, AKI recovery rate in the VA group consisted of 15 (26%) complete recovery and 5 (9%) partial recovery; 1 (2%) remained dialysis-dependent. In the VV group, 22 (43%) had complete recovery (p=0.07), 3(6%) had partial recovery (p=0.72), and 1 (2%) was dialysis-dependent (p>0.99). In-hospital mortality was 64% in the VA group and 49% in the VV group (p=0.13). **Conclusions**: Renal outcomes in critically ill patients who develop AKI are not associated with the type of ECMO used. This serves as preliminary data for future studies in the area.

Keywords: extracorporeal membrane oxygenation, acute kidney injury, treatment outcome, renal replacement therapy, intensive care units

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Introduction

The use of extracorporeal membrane oxygenator (ECMO) has risen for adults and children with severe cardiac and pulmonary dysfunction. Of the two types of ECMO, veno-venous (VV) ECMO is used for respiratory support. In contrast, veno-arterial (VA) ECMO is used for cardiac support [1, 2]. Generally, patients receiving ECMO therapy are critically ill. These patients receive aggressive treatments with nephrotoxic medications, vasopressor support, antibiotics, and intravenous contrast agents that put them at high risk for acute kidney injury (AKI) [3].

Additionally, patients are also exposed to risk factors specific to the ECMO circuit's mechanics that may

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affect renal recovery [4]. The incidence of AKI in patients on ECMO is about 75 to 80% [3, 5, 6]. Several factors related to the intervention of ECMO treatment could contribute to AKI. First, ECMO initiation and subsequent vasopressors' adjustments can cause rapid hemodynamic fluctuations with resultant ischemia-reperfusion-induced AKI [7]. Second, blood exposure to artificial surfaces within the ECMO circuit can cause systemic inflammation [8], hypercoagulation, haemolysis or haemoglobinuria [9]. Finally, hormonal variations, including renin-angiotensin-aldosterone dysregulation, occur in patients receiving ECMO, leading to impaired renal homeostasis and maladaptive hemodynamic fluctuations [4].

Differences in hemodynamic flows and molecular changes between the two types of ECMO circuits may pose different risks of developing or recovering from AKI. Cardiac output in VA ECMO is a varying mixture of pulsatile (native cardiac) and non-pulsatile (ECMO flow) based on the residual function of the heart [10]. On the other hand, patients on VV ECMO have only pulsatile, native cardiac, blood flow [11]. Veno-arterial ECMO is closely related to cardiopulmonary bypass (CPB) [12]. Several studies suggested that the systemic inflammatory response in patients on CPB depends on the nature of the blood flow with pulsatile blood flow having reduced inflammatory response compared to non-pulsatile blood flow in extracorporeal circulation [13]. It has been further theorised that end-organ microcirculation is improved with pulsatile blood flow [14].

Development of AKI is associated with significant morbidity and mortality. Dialysis dependence at ninety-days is as high as 30% and a five-year cumulative risk for developing end-stage renal disease (ESRD) of 11.7% [15]. Mortality of patient developing AKI in an ICU can be greater than 50% [16]. Garzotto et al. showed that out of 576 patients in the ICU 379 developed AKI, 59.4% had a complete renal recovery, 13.5% had a partial renal recovery, and 27.2% of patients did not recover their renal functions at the time of death or ICU discharge. Their study also showed that when AKI patients were compared with non-AKI patients, they had a higher crude ICU mortality (28.8 vs 8.1%; $p<0.001$) and longer ICU length of stay [17]. Given these findings maximising the chance of renal recovery after AKI is of prime importance. Hence, knowledge about the prevalence of renal recovery in patients on ECMO with AKI is valuable in predicting morbidity and mortality.

Renal replacement therapy (RRT) is sometimes required in patients who develop AKI to assist with volume management and metabolic derangements [3]. The combination of ECMO and AKI requiring RRT portends a poorer prognosis, with an in-hospital mortality rate 3.7-fold higher as well as a high risk for the long-term development of CKD or dialysis-dependent renal failure [18, 19]. Antonucci et al. found no significant difference in the intensive care unit (ICU) mortality in ECMO patients with AKI requiring or not requiring RRT. They also found no significant differences in the ICU mortality between VA and VV ECMO patients with AKI [20]. Significantly, short-term renal outcomes in patients who develop AKI have not been compared by type of ECMO support.

The study aimed to analyse and compare renal outcomes in critically ill patients who develop AKI and receive VA or VV ECMO support.

Specifically, the association of complete renal recovery, partial renal recovery, and dialysis dependence at the time of discharge in adult critical care patients with the type of ECMO was assessed.

Material and Methods

Study Population

This is a retrospective single centre study at Wake Forest School of Medicine/Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, USA. This tertiary academic centre consists of 873 beds, and all patients treated with ECMO are housed in the Cardiovascular ICU. Inclusion Criteria:

Inclusion Criteria

- All adults, of 18 years and older, treated with ECMO between January 2015 and June 2019.
- Patients with underlying chronic kidney disease (CKD).
- Patients who developed AKI either before or after ECMO initiation.
- Patients who received VA or VV ECMO during the study period.
- Patients with veno-arterial-venous (VAV) or veno-venous-arterial (VVA) circuit were classified as receiving VA ECMO, as their numbers were low.

Exclusion Criteria

- Patients with a diagnosis of ESRD on admission and those who did not have sufficient data were excluded.

The study was reviewed and approved by the Institutional Review Board of Wake Forest Baptist Medical Center.

Acute Kidney Injury and Renal Replacement Therapy

AKI was defined and classified according to the Acute Kidney Injury Network (AKIN) criteria based on serum creatinine levels [21]. Two nephrologists reviewed the electronic medical charts for AKI staging. The initiation of RRT was at the discretion of the treating nephrologist. While receiving ECMO, all patients who required RRT were prescribed continuous venovenous hemofiltration (CVVH) with NxStage System One™ (NxStage Medical, Inc. Lawrence, MA, USA). After ECMO decannulation, the prescribed RRT was either intermittent haemodialysis (IHD) or CVVH at the discretion of the treating nephrologist.

ECMO

A Cardiohelp System or Rotaflow Console (Getinge, Gothenburg, Sweden) was used for ECMO. Per local standard of care, mean arterial pressure on ECMO was maintained at > 65 mm Hg with the ECMO flow along with additional vasopressors if needed. The haemoglobin goal for patients on ECMO was ≥ 10.0 g/dl.

Data Collection

Standard procedural technology (CPT) codes (33946, 33947, 33948, 33949) were used to identify patients who received ECMO.

The following demographics were recorded: age, sex, race, BMI, type of ECMO; comorbidities:

Comorbidities: diabetes, hypertension, hyperlipidaemia, CKD, chronic obstructive pulmonary disease, coronary artery disease, smoking history.

Other: length of ICU stay.

For renal outcomes, baseline serum creatinine, peak serum creatinine during the hospitalisation, the timing of AKI diagnosis, i.e.(before or after ECMO initiation), and serum creatinine on the day of discharge, were collected.

Risk factors for AKI, such as the use of vasopressors, diagnosis of sepsis, presence of shock, use of non-steroidal anti-inflammatory drugs (NSAIDs), iodinated IV contrast, congestive heart failure (CHF), nephrotoxic antibiotics, and CPB were recorded for all AKI patients.

The severity of illness was assessed using serum lactic acid level, Charlson Comorbidity Index (CCI) [22] and Acute Physiology, Age and Chronic Health Evaluation (APACHE) II score [23].

Outcomes

Patients treated with ECMO who developed AKI during hospitalisation had their renal function monitored throughout the hospitalisation period. For these patients, the renal outcomes were classified as complete renal recovery, partial renal recovery, and dialysis-dependent at the time of discharge, based on definitions used in previous studies [15].

All the deaths that occurred during the hospitalisation period were recorded.

Complete renal recovery was defined as the patient's serum creatinine returning to the baseline value.

Partial renal recovery was defined as an improvement in the patient's serum creatinine but not returning to baseline at the time of discharge [15].

Dialysis dependency was defined as the patient still requiring RRT (intermittent hemodialysis) at the time of discharge.

Statistical Analysis

Summary statistics, including means and standard deviations for continuous data and frequencies and proportions for categorical measures, were calculated for all study variables. Group differences were assessed using Fisher's exact tests for categorical data and independent t-tests for continuous outcomes. Logistic regression models were created to estimate the odds ratio and corresponding 95% confidence intervals.

The significance level for all analyses was set at $\alpha = 0.05$.

The SAS (version 9.4, Cary, NC, USA) was used for all analyses.

Results

Patients

A total of 125 patients received treatment with ECMO between January 2015 and June 2019. Three patients were excluded from the cohort (1 patient had ESRD, and

two patients had insufficient data). Of the 122 patients, 64 received VA ECMO, and 58 received VV ECMO.

Of the 64 patients who received VA ECMO, 56 received it for cardiogenic shock, 6 for unspecified shock and 2 for extracorporeal cardiopulmonary resuscitation and among the 58 in VV ECMO group 12 for sepsis, 15 for pneumonia (including viral), 10 for trauma and 21 for other causes of ARDS. The most common primary diagnosis in the VA group was acute coronary syndrome followed by CHF, cardiac arrest, sepsis and pulmonary embolism. The most common primary diagnosis in the VV group was sepsis, followed by pneumonia, trauma and viral pneumonia (Supplemental Table 1). Table 1 presents the baseline characteristics of the study cohort.

The mean (standard deviation) age in the VA group was 55.4(15.8) years and 42.9(16.2) years in the VV group (p<0.0001). The distribution of sex, BMI and race were similar between the two groups. Except for CAD, which was more prevalent in the VA ECMO group (p=0.023), the prevalence of other coexisting conditions and CCI were similar between the two groups.

The average APACHE II scores were higher in the VV ECMO group compared to VA ECMO group (28.0 [6.2] vs 24.8 [7.9], respectively, p=0.014), while the average serum lactic acid levels were higher in the VA ECMO group (7.4 [4.4] mmol/L vs 4.4 [3.2] mmol/L, respectively, p=0.0002).

Using a propensity-matched analysis for both the groups, there was no difference in renal recovery outcomes at the time of discharge.

The average ICU length of stay was longer in the VV ECMO group, 24 days in the VV ECMO group vs 12 days in the VA ECMO group. (p<0.0001).

Incidence of AKI

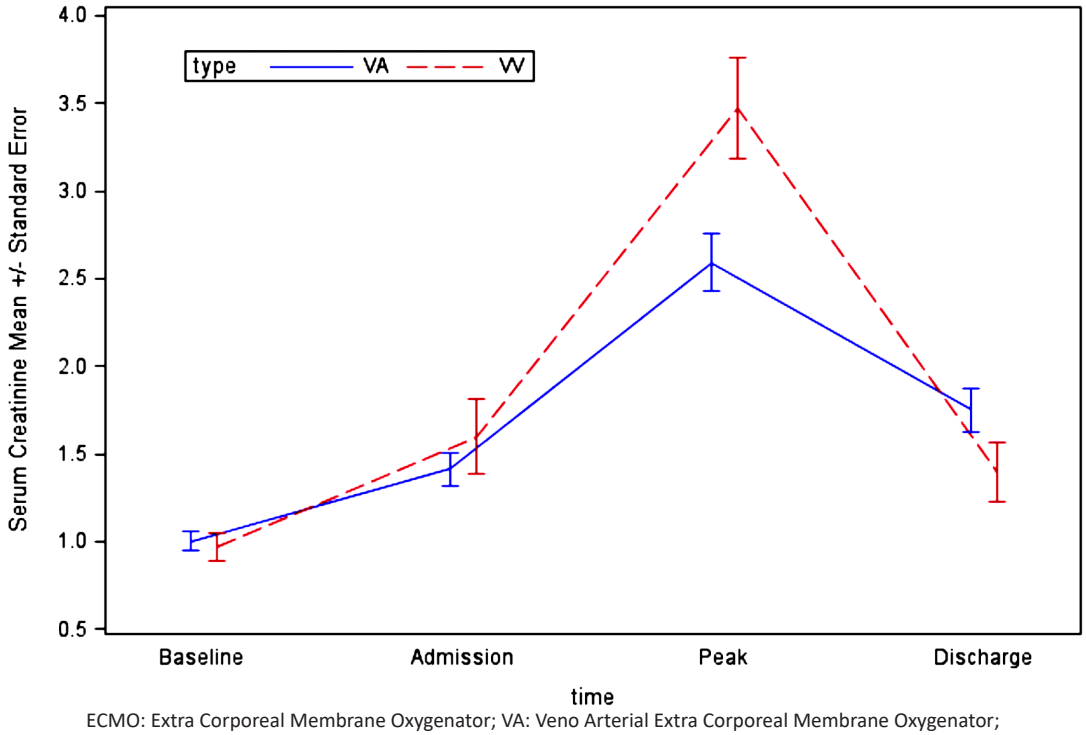
A total of 109(89%) patients developed AKI. Of these, 58(91%) were treated with VA ECMO, and 51(88%) were treated with VV ECMO. In the VA ECMO group, 16 (28%) patients developed stage 1 AKI, 10(17%) patients developed stage 2 AKI, and 32(55%) patients developed stage 3 AKI. A total of 27(47%) patients required RRT. In the VV group, 10(20%) patients had stage 1 AKI (p=0.37), 1(2%) patient had stage 2 AKI (p=0.0096), 40(78%) patients had stage 3 AKI (p=0.015), and 38 (75%) patients required renal replacement therapy (p=0.0035). The baseline serum creatinine was similar, but patients in the VV ECMO group had higher peak serum creatinine levels before RRT initiation (Figure 1).

In our cohort, most patients who developed AKI reached stage 3 AKI. Though both groups had similar baseline characteristics, comorbidities, and CCI, there were higher rates of stage 3 AKI, and the use of RRT in the VV ECMO group (Figure 2).

Table 1. Baseline Patient Characteristics by Type of ECMO Support

	VA ECMO	VV ECMO	p-Value
Total Number	64	58	
Age, mean (SD), years	55.4 (15.8)	42.9 (16.2)	<0.0001
Male sex, n (%)	50 (78%)	40 (70%)	0.21
White race, n (%)	46 (79%)	36 (71%)	0.37
BMI, mean (SD)	32.9 (9.0)	30.4 (8.1)	0.30
Smoking – No	59 (92%)	49 (84%)	0.26
Diabetes mellitus, n (%)	4 (6%)	6 (10%)	0.52
CAD, n (%)	14 (22%)	4 (7%)	0.023
HTN, n (%)	16 (25%)	15 (26%)	>0.99
CKD, n (%)	10 (16%)	3 (5%)	0.080
Hyperlipidaemia, n (%)	14 (22%)	5 (9%)	0.049
COPD, n (%)	7 (11%)	6 (10%)	>0.99
APACHE II, mean (SD)	24.8 (7.9)	28.0 (6.2)	0.014
Charlson Comorbidity Index, mean (SD)	2.4 (2.7)	1.8 (3.0)	0.27
Lactic acid, mean (SD), mmol/L	7.4 (4.4)	4.4 (3.2)	0.0002
ICU length of stay, mean (SD), days	11.6 (10.8)	24.5 (15.4)	<0.0001
AKI, all stage, n (%)	58 (91%)	51 (88%)	0.77

SD – Standard Deviation, ECMO - Extra Corporeal Membrane Oxygenator, VA ECMO – Veno Arterial Extra Corporeal Membrane Oxygenator, VV ECMO – Veno Venous Extra Corporeal Membrane Oxygenator, CAD – Coronary Artery Disease, HTN- Hypertension, CKD – Chronic Kidney Disease, CHF – Congestive Heart Failure, COPD – Chronic Obstructive Pulmonary Disease, APACHE II - Acute Physiology, Age and Chronic Health Evaluation II, ICU – Intensive Care Unit, AKI – Acute Kidney Injury, RRT – Renal Replacement Therapy

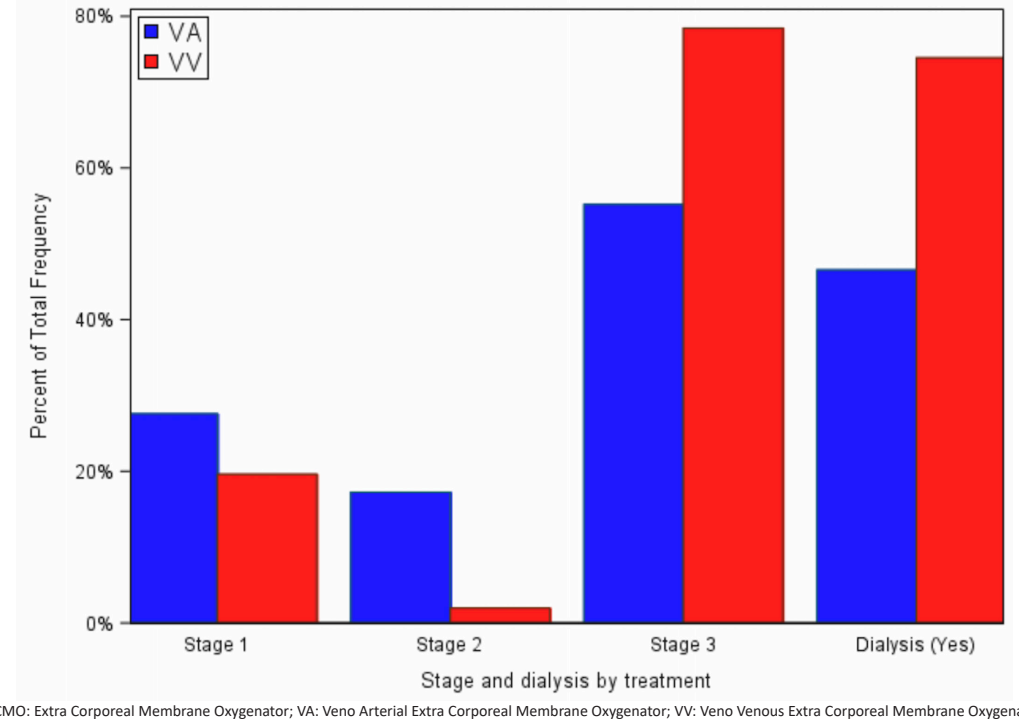


ECMO: Extra Corporeal Membrane Oxygenator; VA: Veno Arterial Extra Corporeal Membrane Oxygenator; VV: Veno Venous Extra Corporeal Membrane Oxygenator

Fig.1. Trends in mean serum creatinine by type of ECMO support

Distribution of AKI Risk Factors

The exposure to factors that might contribute to AKI development (Table 2) was also analysed. The Odds ratios (OR) were calculated with the VA as the reference group. IV contrast, use of NSAIDs, nephrotoxic antibiotics, vasopressors, CHF, and shock diagnosis were not statistically different between the two groups. The use of CPB was 24% in the VA group and 2% in the VV group (p=0.0088) which calculated to OR for AKI of 15.9(2.0, 125.9). The prevalence of sepsis diagnosis was 9% in



ECMO: Extra Corporeal Membrane Oxygenator; VA: Veno Arterial Extra Corporeal Membrane Oxygenator; VV: Veno Venous Extra Corporeal Membrane Oxygenator

Fig. 2. Stages of acute kidney injury by type of ECMO support

Table 2 - Distribution of Acute Kidney Injury Risk Factors

Factor	VA ECMO	VV ECMO	Odds Ratio of AKI (95% CI)	p-value
IV contrast scan (%)	37 (64%)	33 (65%)	0.96 (0.44, 2.11)	0.92
Cardiopulmonary Bypass (%)	14 (24%)	1 (2%)	15.9 (2.0, 125.9)	0.0088
NSAID (%)	9 (16%)	15 (29%)	0.44 (0.17, 1.12)	0.085
Antibiotics (%)	32 (55%)	29 (57%)	0.93 (0.44, 1.99)	0.86
Sepsis (%)	5 (9%)	12 (24%)	0.31 (0.10, 0.94)	0.039
Hypotension (%)	49 (84%)	35 (69%)	2.49 (0.99, 6.28)	0.053
Vasopressor dependent Hypotension (%)	38 (66%)	31 (61%)	1.23 (0.56, 2.68)	0.61
CHF (%)	14 (24%)	10 (20%)	1.31 (0.52, 3.26)	0.57

VA ECMO – Veno Arterial Extra Corporeal Membrane Oxygenator, VV ECMO – Veno Venous Extra Corporeal Membrane Oxygenator, AKI – Acute Kidney Injury, CHF – Congestive Heart Failure, NSAID – Non-Steroidal Anti Inflammatory Drugs

the VA group and 24% in the VV group (p=0.039), suggesting that use of VA ECMO might yield lower risk of AKI than the use of VV ECMO in patients with sepsis, with OR for AKI of 0.31(0.10, 0.94).

Renal Outcomes

Of the 58 patients who developed AKI in the VA ECMO group, 15(26%) had a complete renal recovery, 5 (9%) had a partial renal recovery, and 1 (2%) was dialysis-dependent at the time of discharge (Table 3). Of the 51 patients who had AKI in the VV ECMO group, 22 (43%) had complete renal recovery (p = 0.07), 3(6%) had partial renal recovery (p=0.72), and 1 (2%) was dialysis dependent on the date of discharge (p>0.99). Mortality was 64% among patients who developed AKI in the VA group and 49% among patients who developed AKI in the VV group (p=0.13).

Discussion

AKI is a common complication in critically ill patients. It portends a significant risk for short- and long-term mortality, CKD development, and cardiovascular events [15]. After an episode of AKI, the rate of dialysis dependence requiring RRT ranges from 0 to 40% [24, 25]. Hence, it is crucial to reduce the exposure to factors that may contribute to the development of AKI and focus on maximising the chance of renal recovery after AKI. In our study, of the 122 critically ill patients treated with ECMO, 109 (89%) developed AKI during the hospitalisation, which is similar to the reported incidence of 75 to 80% AKI in patients on ECMO [3]. Chen *et al.* evaluated long term outcomes in 3251 patients with AKI who received ECMO. In their cohort, complete renal recovery, partial renal recovery, and dialysis dependence occurred in 48.4%, 32.6% and 19% of the patients [19]. Our study is the first to evaluate the renal outcomes by type of ECMO support. We found that the overall AKI incidence and renal recovery rate did not differ by type of ECMO support.

In regards to AKI, the baseline serum creatinine was identified as the most recent serum creatinine before admission or serum creatinine at the time of admission if no previous labs were available and the estimated glomerular filtration rate (eGFR) was reported using the CKD-EPI equation [26]. The presence of other risk factors for AKI and their association with a renal outcome such as the use of IV contrast [27], NSAIDs [28], CPB machine [29], nephrotoxic antibiotics [30], sepsis [31], CHF [32] and vasopressors-dependent hypotension were also evaluated in the present study [33]. The diagnosis of sepsis was statistically more common in the VV ECMO group. This could account for the higher incidence of stage 3 AKI and RRT's need in this group. The higher RRT rates in VV ECMO group are due to the higher number of Stage 3 AKI compared to the VA ECMO group. It was noted that patients in the VV ECMO group had longer ICU length of stay, likely related to differences in the primary clinical indication for ECMO initiation. There was no significant differ-

Table. 3. Renal Outcomes by Type of ECMO Support

	VA ECMO	VV ECMO	p-value
Complete Renal Recovery	15 (26%)	22 (43%)	0.07
Partial Renal Recovery	5 (9%)	3 (6%)	0.72
Dialysis Dependent	1 (2%)	1 (2%)	>0.99
Death	37 (64%)	25 (49%)	0.13

ECMO - Extra Corporeal Membrane Oxygenator, VA ECMO – Veno Arterial Extra Corporeal Membrane Oxygenator, VV ECMO – Veno Venous Extra Corporeal Membrane Oxygenator

ence between the two ECMO groups concerning the distribution of AKI risk factors such as use IV contrast, NSAIDs, nephrotoxic antibiotics, CHF, hypotension and vasopressor-dependent hypotension. Though the baseline serum creatinine was similar between the groups, patients in the VV ECMO group had higher peak serum creatinine levels before RRT initiation (Figure 1). This might be related to the indication for RRT; those with VA ECMO may have had more volume overload as the indication for dialysis instead of solute clearance, making it difficult to draw firm conclusions on kidney injury potential between ECMO groups based on comparison of serum peak creatinine values alone.

In the present study, the complete renal recovery rate was not statistically different between the two ECMO groups. Though VV ECMO group had higher APACHE II scores, stage 3 AKI, and need for RRT; 43% in the VV ECMO group had complete renal recovery relative to 26% of patients in the VA ECMO. The cardiac output in VA ECMO is non-pulsatile or a mixture of pulsatile and non-pulsatile flow. The VA setting improves the total cardiac output. It facilitates renal blood flow [34].

On the other hand, in VV ECMO, systemic oxygenation and delivery are improved, contributing to better renal metabolism [3]. The rates of partial renal recovery and dialysis dependency at the discharge time were similar in both ECMO groups. The difference in the rate of complete renal recovery could be related to our primary hypothesis that the pulsatile blood flow with VV ECMO renders renal hemodynamics closer to physiologic [14]. These findings need to be interpreted with caution, given the smaller sample size. The results serve as preliminary data for more extensive studies.

We noted that serum lactic acid levels were significantly higher in the VA ECMO. Previous studies showed that higher lactic acid levels are directly associated with higher hospital mortality [35]. Though in-hospital mortality for patients who developed AKI on ECMO was not statistically different between the groups possibly due to small sample size, the VA ECMO group had 66% mortality rate compared to 49% in the VV ECMO group. Serum lactic acid levels did not correlate with renal outcomes in our cohort. We noted overall in-hospital mortality of 57% for patients who developed AKI and were treated with ECMO, similar to that reported by Antonucci et al. [20]. The use of CPB machine is also a known risk factor for AKI [29]. In the present study, although CPB was more commonly used in the VA ECMO group, as these patients had a primary cardiac need for ECMO support, renal outcomes were not impacted by CPB use.

Conclusion

No significant differences in the extent of renal recovery, varying from complete to partial and dialysis dependency between the patients who develop AKI and treated with VV or VA ECMO, were observed.

While clinicians should be cautious interpreting this data, future research in this field on larger collaborative multi-institutional cohorts is needed to understand renal outcomes in patients undergoing extracorporeal oxygenation.

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Conflict of interest

None to declare.

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Supplemental Table 1. Primary Diagnosis of VA and VV ECMO groups

Primary Diagnosis	VA ECMO	VV ECMO
Acute Coronary Syndrome	27	0
Congestive heart failure	9	0
Sepsis	5	12
Cardiac arrest	5	0
Valvular heart disease	4	0
Pulmonary embolism	3	0
Cardiac arrhythmias	3	0
Others	8	15
Pneumonia	0	10
Trauma	0	10
Viral Pneumonia	0	5
Drug Overdose	0	3
Acute Pancreatitis	0	2
Asthma	0	1

VA ECMO – Veno Arterial Extra Corporeal Membrane Oxygenator, VV ECMO – Veno Venous Extra Corporeal Membrane Oxygenator. Others in the VA ECMO group include heart transplant, thyrotoxicosis, non-ischemic cardiomyopathy, aortic dissection, calcium channel blocker overdose, ventricular septal defect and myocarditis. Others in the VV ECMO group include hemothorax, lung contusion, vasculitis, sickle cell acute chest syndrome and pulmonary neoplasm.