ORIGINAL ARTICLE

# Acute Kidney Injury in Patients Undergoing Extracorporeal Membrane Oxygenation: A Retrospective Cohort Study

Aswin Surjit[1], Bipi Prasannan[2], Jobin Abraham[3], Anuroop Balagopal[4], Vavullipathy Narayanan Unni[5]

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## Abstract

**Aims and background:** Extracorporeal membrane oxygenation (ECMO) is a mode of extracorporeal therapy to support oxygenation of patients with severe cardiac or respiratory failure. Studies have shown that acute kidney injury (AKI) can worsen the outcome in these patients. This study aims to assess the incidence and outcome of AKI in patients on ECMO support.

**Materials and methods:** This retrospective study included 64 patients who underwent ECMO for more than 24 hours. Patients who died within 48 hours of initiation of ECMO and patients with end-stage renal disease (ESRD) on maintenance hemodialysis were excluded. Acute kidney injury was diagnosed and categorized according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria.

**Results:** Of the 64 patients studied, 38 patients (59.38%) developed AKI and 17 patients (44.73%) among them developed AKI within 24 hours of initiation of ECMO. Age, Acute Physiology and Chronic Health Evaluation (APACHE-II) score, hypertension, use of nephrotoxic agents, inotropic support, and poor cardiac function were the risk factors associated with the development of AKI. Diabetes mellitus, type of ECMO used, and duration of ECMO were not found to be risk factors for AKI. Renal replacement therapy was initiated in 31 patients (81.58%). The overall mortality in the whole group was 67.19%, while it was 81.58% among the patients with AKI.

**Conclusion:** Acute kidney injury was found to be an independent risk factor for mortality in patients on ECMO. Early identification of the risk factors for AKI and management may help to improve the survival rate.

**Clinical significance:** The occurrence of AKI among patients on ECMO support increases the risk of mortality significantly. Hence, measures to prevent AKI, as well as early detection and appropriate management of AKI, would improve patient outcomes.

**Keywords:** Acute kidney injury, Acute respiratory distress syndrome, Continuous renal replacement therapy, Cohort study, Extracorporeal membrane oxygenation, Renal replacement therapy.

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## Highlights

Prevention and early detection of acute kidney injury (AKI) in patients on extracorporeal membrane oxygenation (ECMO) are essential to improve outcome.

## Introduction

Extracorporeal membrane oxygenation is a major lifesaving treatment modality in those with potentially reversible severe cardiac or respiratory failure.[1] The CESAR trial has shown survival benefits with ECMO when compared with conventional ventilator support in such patients.[2] Based on the vascular access, ECMO has been classified into venoarterial (VA) and venovenous (VV) ECMO. The VA ECMO is used in patients requiring cardiac support, as in cases of cardiogenic shock, cardiac arrest, or postcardiac surgery.[3] The venovenous ECMO (VV-ECMO) is used in patients having acute respiratory failure, pneumonia-related acute respiratory distress syndrome (ARDS), post lung transplant failure, or trauma to the thorax causing respiratory failure.[4]

Acute kidney injury can occur in ECMO patients, with an incidence of 61% and 46% in VA-ECMO and VV-ECMO, respectively.[5,6] The mortality associated with VA-ECMO (40–60%) is reported to be more when compared with VV-ECMO (21–37%).[7,8] The etiological factors causing AKI in patients receiving ECMO include factors like decreased perfusion, low oxygenation, loss of autoregulation, carbon dioxide retention, accumulation of nephrotoxins, and sepsis; ECMO circuit-related factors include, type of ECMO, positive end-expiratory pressure, blood shear stress, and thromboembolism.[9,10]

[1]Department of Internal Medicine, Aster Medcity, Kochi, Kerala, India

[2,5]Department of Nephrology, Aster Medcity, Kochi, Kerala, India

[3,4]Department of Critical Care, Aster Medcity, Kochi, Kerala, India

**Corresponding Author:** Vavullipathy Narayanan Unni, Department of Nephrology, Aster Medcity, Kochi, Kerala, India, Phone: +91 9847049857, e-mail: unnivn1@gmail.com

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**Conflict of interest:** None

The study aims to analyze the incidence and risk factors of AKI in ECMO and its impact on mortality.

## Materials and Methods

This is a retrospective study conducted at a quaternary care center in South India from February 2015 to March 2023. The study was done with permission from the hospital ethics committee (ref. no. AM/EC/246-2022). The study included all patients who underwent ECMO for over 24 hours at our institution. The study excluded those who died within 48 hours of initiating ECMO and those who were on maintenance hemodialysis.

The demographic and clinical data were obtained from the electronic medical records. The medication history, including

the nephrotoxic drugs received by the patient before and after ECMO initiation, was also collected. The indication for ECMO, type of ECMO, duration of ECMO in days, and vascular access for ECMO were determined. Acute Physiology and Chronic Health Evaluation (APACHE-II) score was used to assess the severity of illness. Those with less than 40% left ventricular ejection fraction (LVEF) on echocardiogram were considered to have poor cardiac status. Kidney Disease Improving Global Outcomes (KDIGO) criteria was used to define AKI, staging and recovery of AKI, and chronic kidney disease (CKD).[11,12] The details of renal replacement therapy (RRT), including the type of RRT, the number of sessions planned, fluid removal achieved, and the requirement of inotropic support, were recorded.

The primary objective of the study was to determine the incidence of AKI in patients undergoing ECMO. The secondary objectives were to analyze the risk factors and characteristics of AKI.

### Statistical Analysis

R software (version 4.1.1) was used for statistical analysis. Mean and standard deviation were used to describe quantitative variables, while percentage distribution was used to describe qualitative variables. Independent sample *t*-test and Chi-square test were used to compare quantitative variables and discrete variables between groups, respectively. To analyze the effects of outcome and predictive variables, binary logistic regression was used. $p < 0.05$ was taken to be significant.

## Results

The study had 64 eligible patients with 35 males and 29 females in the age range of 4 months–73 years (mean age, 42.58 ± 18.63 years). Among them, 43 patients (67.19%) had an APACHE-II score above 25. A good LVEF was found in only 26 patients (40.63%). Venoarterial ECMO was done in 35 patients (54.69%), and venovenous ECMO in 29 patients (45.31%). The indication for VA-ECMO included severe left ventricular dysfunction/heart failure (*n* = 14, 40.00%), cardiac arrest (*n* = 7, 20.00%), support for cardiac surgery (*n* = 7, 20.00%), cardiogenic shock (*n* = 3, 8.57%), and myocarditis (*n* = 4, 11.43%). The indication for all patients on VV-ECMO was ARDS, of which 16 patients (55.17%) had Coronavirus disease of 2019 (COVID-19) infection as the cause for ARDS.

The minimum duration of ECMO was 2 days, and the maximum was 33 days (mean duration of ECMO 6.60 ± 5.6 days). Of the patients who underwent ECMO, AKI occurred in 38 patients (59.38%), 17 patients (44.73%) developed AKI on the first day after initiating ECMO, 10 patients (26.33%) developed AKI on the second day, three patients (7.89%) developed AKI on the third day, three patients (7.89%) developed AKI between the fourth and seventh day, and five patients (13.16%) developed AKI after 7 days of initiation of ECMO. Table 1 compares the characteristics of ECMO patients who had AKI with the non-AKI group. Three patients had acute on CKD following ECMO initiation.

The etiology of AKI was sepsis (*n* = 24, 63.16%), septic shock (*n* = 6, 15.79%), cardio renal syndrome (*n* = 7, 18.42%), and pulmonary renal syndrome (*n* = 1, 2.63%). Among the patients who developed AKI, nine patients (23.68%) had stage-I AKI, 20 patients (52.64%) had stage-II AKI, and 9 patients (23.68%) had stage-III AKI.

Thirty-one patients (81.58%) who had AKI needed dialysis. The indications for RRT were oliguria/volume overload (*n* = 15, 48.39%), anuria (*n* = 10, 32.26%), refractory hyperkalemia (*n* = 2, 6.45%), and severe metabolic acidosis (*n* = 4, 12.90%). The initial mode of RRT used was sustained low-efficiency dialysis (SLED) in 18 patients (58.06%), continuous renal replacement therapy (CRRT) in 12 patients (38.71%), and peritoneal dialysis in one patient (03.23%). Among the 12 patients who underwent CRRT, only four patients (33.33%) could complete the planned hours of dialysis: one patient survived and three patients were converted to SLED. Of those patients who were on CRRT, eight patients (66.67%) had premature termination due to clotting of the extracorporeal circuit (*n* = 1,12.50%), hypotension (*n* = 3, 37.50%), or death (*n* = 4, 50.00%). Among the 21 patients who underwent SLED (including the three patients who were converted to SLED from CRRT), nine patients (42.86%) could complete the planned SLED sessions, and two patients (9.52%) were converted to conventional hemodialysis. A total of 70 SLED sessions were planned for the 21 patients, and 59 sessions were completed successfully, achieving 82.52% of the target fluid removal. The reasons for premature termination of SLED among 10 patients (47.62%) were also the same, clotting of the extracorporeal circuit (*n* = 1, 10.00%), hypotension (*n* = 2, 20.00%), or death (*n* = 7, 70.00%). The two patients who underwent conventional hemodialysis completed the 20 planned hemodialysis sessions.

Inotropic support was increased in 24 patients (77.42%) after they were initiated on RRT. Recovery of renal functions was observed in six patients (15.79%) among the 38 patients with AKI,

**Table 1:** Risk factors for acute kidney injury

| *Patient characteristics* | *AKI during ECMO (n = 38)* | *No AKI during ECMO (n = 26)* | *p-value* |
|---|---|---|---|
| Age group | | | |
| <18 years | 3 | 6 | 0.02*[a] |
| 18–60 years | 24 | 19 | |
| >60 years | 11 | 1 | |
| Hypertension | | | |
| Yes | 13 | 3 | 0.04*[b] |
| No | 25 | 23 | |
| Nephrotoxic drugs | | | |
| Yes | 25 | 9 | 0.007*[a] |
| No | 13 | 17 | |
| Cardiac status | | | |
| Good >55% | 9 | 17 | 0.002*[b] |
| Moderate 40–55% | 8 | 3 | |
| Poor <40% | 21 | 6 | |
| Inotropic support | | | |
| Yes | 31 | 11 | 0.01*[a] |
| No | 7 | 15 | |
| APACHE-II score | 26.12 ± 4.02 | 22.54 ± 3.95 | 0.003*[c] |
| Diabetes mellitus | | | |
| Yes | 10 | 6 | 1.00[b] |
| No | 28 | 20 | |
| Type of ECMO | | | |
| Veno-arterial | 24 | 11 | 0.09[a] |
| Veno-venous | 14 | 15 | |
| Total ECMO days | 6.27 ± 4.41 | 6.96 ± 6.73 | 0.67[c] |

[a]Chi-square test, [b]Fisher exact test, [c]*t*-test; *Statistically significant variables – age, hypertension, nephrotoxic drugs, inotropic support, and APACHE-II score; AKI, acute kidney injury; APACHE-II, Acute Physiology and Chronic Health Evaluation score; ECMO, extracorporeal membrane oxygenation

**Table 2:** Risk factors for mortality

| *Characteristics* | *Non-survivor* | *Survivor* | *p-value* |
|---|---|---|---|
| Inotropic support | | | |
| Yes | 33 | 8 | 0.002[a] |
| No | 10 | 13 | |
| APACHE-II score | 25.93 ± 3.38 | 22.10 ± 4.67 | 0.001[b] |
| AKI | | | |
| Yes | 31 | 7 | 0.003[a] |
| No | 12 | 14 | |
| RRT | | | |
| Yes | 27 | 4 | 0.001[a] |
| No | 16 | 17 | |
| Duration of ECMO till AKI (days) | 4.16 ± 4.49 | 2.86 ± 1.07 | 0.002[b] |

[a]Chi-square test, [b]*t*-test; Of the 64 patients who underwent ECMO, 43 patients (67.19%) died. All these variables were found to be significant risk factors for mortality; AKI, acute kidney injury; APACHE-II, Acute Physiology and Chronic Health Evaluation score; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy

of which three patients had complete recovery of renal function. Of the remaining 32 patients (84.21%) who did not recover from AKI, one patient became dialysis-dependent, and the remaining ($n = 31$) succumbed to death.

Among the 64 patients who underwent ECMO therapy, 43 patients (67.19%) succumbed to death while on ECMO therapy. The mortality among the patients who developed AKI was 81.58% (31 deaths), of which 27 patients (87.10%) were on RRT and four patients (57.14%) were not on RRT. Table 2 shows the association of risk factors with mortality. The odds ratio was 4.89 for mortality associated with AKI. The mortality among patients who were initially initiated on CRRT and SLED was 91.67% (11 patients) and 72.22% (13 patients), respectively. However, the modality of RRT did not influence the survival of patients ($p = 0.19$). The cause of death among patients who underwent ECMO was attributed to sepsis and septic shock in 19 patients (44.19%), cardiogenic shock and cardiac arrest in 14 patients (32.55%); the remaining 10 patients (23.26%) died due to ARDS, diffuse alveolar hemorrhage, refractory shock, acute myocardial infarction, low cardiac output syndrome, recurrent arrhythmia, stroke, or acute liver failure.

## Discussion

Our study was aimed at determining the incidence and the associated risk factors for AKI in those who underwent ECMO. Data from previous studies have shown that 26–85% of patients who underwent ECMO developed AKI.[10] This wide range was attributed to varying patient characteristics and the study setting.[13,14] Our study population also showed a higher incidence of AKI (59.38%). Acute kidney injury developed as early as within 24 hours of initiation of ECMO in 57% and 85% of the patients in studies done by Schmidt et al. and Tsai et al., respectively.[15,16] During the process of ECMO, patients can have ischemic reperfusion injury due to the restoration of microcirculation to the hypo-perfused tissues, leading to an early onset of AKI.[17] In our study, even though there is a high incidence of AKI, only 44.73% had developed AKI within 24 hours of ECMO initiation. There is a lack of evidence on whether the duration of ECMO is a risk factor for developing AKI. In our study, the duration of ECMO and AKI did not have any association.

Data from previous studies suggest that the pulsatility and circuit pressures of ECMO, renal hypoxia, use of diuretics and vasopressors, etc., may contribute to hemodynamic instability, leading to renal microcirculation disturbance and reduced glomerular filtration.[18–20] In our study too, increasing age, high APACHE-II score, use of nephrotoxic drugs, low cardiac output, and need for inotropic support were found to increase the risk of developing AKI. Our study did not reveal any difference in association on the type of ECMO and risk of developing AKI. There are studies that reported higher risk of AKI with VA-ECMO when compared with VV-ECMO, hence more studies are required to conclude.[21]

Systemic hypertension and diabetes mellitus were the most common comorbidities in our population. In general, hyperglycemic milieu promotes renal mesenchymal transition with fibrosis of endothelial cells contributing to AKI among patients undergoing ECMO. A meta-analysis done by Mou Z et al. suggests that vascular diseases and diabetes mellitus are contributors to AKI in patients undergoing ECMO.[21] In this analysis, hypertension was associated with the risk for development of AKI, while diabetes mellitus was not, this could possibly be due to an inadequate number in our study population.

The major indication for RRT in AKI among our patients was fluid overload. The fluid overload was due to large volumes of intravenous fluid and blood transfusions required during ECMO. The types of RRT used in most of our patients were SLED and CRRT. In our study, there was no association with mortality and modality of RRT used. The recovery of renal function in patients who had AKI was only 19.2%. A study conducted by Bobba A et al. showed that major adverse kidney events (MAKE) could affect the reversibility of AKI and could increase the mortality.[22]

In a study reported by Kielstein et al. and Lee et al., the 90-day survival of patients who developed AKI during ECMO ranged between 20 and 40%.[23,24] A 90-day follow-up was not done in our study; we only studied in-hospital complications and mortality. In-hospital mortality among our patients who underwent ECMO therapy was 67.19%. It is reported that AKI and RRT are two independent risk factors for mortality.[24,25] The requirement for inotropic support, high APACHE-II score, early-onset AKI, severity of AKI, and need for RRT was found to be associated with high risk of mortality. In this study, mortality among patients with severe AKI requiring RRT was higher (87.10%) when compared with those who did not need RRT. Hence, our study also suggests that AKI and the need for RRT are independent risk factors for mortality.

Our single-center study was a retrospective one. We did not study long-term complications; hence, the long-term outcome of those who survived is unknown. The study is one of the few original studies available from Indian population on this topic till date. The study compares the prevalence and association of risk factors for AKI in patients who underwent ECMO therapy in our population.[26–28]

## Conclusion

The study showed a higher risk of developing AKI within 72 hours of initiation of ECMO and was not related to the type of ECMO. The combination of ECMO and AKI dramatically increased mortality, hence, preventing AKI might have a significant impact on survival. Renal replacement therapy in AKI was found to be an independent risk factor for in-hospital death. The main indication for RRT was fluid overload, hence, appropriate use of diuretics and proper fluid management is recommended.

## Clinical Significance

The occurrence of AKI among patients on ECMO support increases the risk of mortality significantly. Hence, measures to prevent AKI, as well as early detection and appropriate management of AKI, would improve patient outcome.

## Orcid

*Aswin Surjit* https://orcid.org/0009-0001-3188-4158
*Bipi Prasannan* https://orcid.org/0009-0006-7216-6562
*Jobin Abraham* https://orcid.org/0000-0002-8854-9748
*Anuroop Balagopal* https://orcid.org/0000-0003-4701-527X
*Vavullipathy Narayanan Unni* https://orcid.org/0009-0006-7701-2669

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