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Original Article

Acute kidney injury in patients receiving ECMO: risk factors and outcomes

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Abstract: Objective: Acute kidney injury (AKI) is common in patients on extracorporeal membrane oxygenation (ECMO) support. Studies focusing on AKI in conjunction with ECMO have had varying results. We aimed to explore the risk factors for in-hospital mortality and AKI in our cohort of adult patients requiring ECMO support. Methods: A retrospective, single-center study enrolling 71 patients was performed. AKI was defined according to Acute Kidney Injury Network (AKIN) criteria.The association between demographics and variables associated with ECMO, AKI,and in-hospital mortality were analyzed. Results: Of the 71 patients, 32 (45.1%) survived to hospital discharge and 52 (73.2%) developed AKI. In the non-survivor group, there were more venoarterial (VA) cases (30/39 vs. 16/32) and longer intensive care unit (ICU) stays (24.3±1.9 vs. 18.0±7.3). Multivariate Cox-proportional hazard analysis also showed that ECMO configuration and length of ICU staywere associated with in-hospital mortality. AKI patients had longer ICU stays (23.3±10.2 vs. 16.4±7.1) and required more blood transfusions (18.5±8 vs. 8±2.3) than non-AKI patients. The maximum serum creatinine (sCr) level during ECMO was significantly higher in AKI than non-AKI patients (196.0±65.1 vs. 132.4±23.4). Multivariate logistic regression analysis showed VA configuration, length of ICU stay, and infection to be significant risk factors for developing AKI. Conclusions: VA ECMO mode and length of ICU stay were associated with in-hospital mortality. VA ECMO mode, length of ICU stay, red blood cell transfusion, sCr level, and infection were significantly associated with AKI.

Keywords: Acute kidney injury, extracorporeal membrane oxygenation, mortality, risk factor

Introduction

Extracorporeal membrane oxygenation (ECMO) is an effective therapy for patients with reversible cardiac and/or respiratory failure who respond poorly to conventional treatments. It is not a definitive treatment, but provides temporary circulatory and respiratory support while organ function is recovering [1-5]. ECMO was first performed in the 1970s and has been increasingly used since the H1N1 pandemic and publication of CESAR trial outcomes in 2009 [6, 7]. ECMO can be performed in two configurations: venovenous (VV) for ventilatory support and venoarterial (VA) for respiratory and cardiac support.

Patients on ECMO often have other organ dysfunction, which may be due to low cardiac output and hypoxemia prior to ECMO initiation [8-10]. Moreover, ECMO, although providing better organ perfusion, is often complicated by the systemic inflammatory response that contributes to worsening organ dysfunction [11, 12]. Acute kidney injury (AKI) is common in patients on ECMO, with an incidence as high as 85% [13, 14]. Some studies have shown that AKI is associated with increased mortality during ECMO [15]; however, controversy exists and although risk factors associated with AKI during ECMO have been studied, no consensus has been achieved [9-11]. We aimed to evaluate the risk factors for in-hospital mortality and AKI in adult patientson ECMO, in a single center over a 10-year period.

Materials and methods

Study population

We performed a retrospective cohort study of 71 adult patients (≥19 years old) who received ECMO support at Shanghai Chest Hospital between January 2006 and December 2015.

All the medical cases involving ECMO support were reviewed (n=74) except some patients were excluded if they were on ECMO for <24 h, if they had end-stage renal disease or serum creatinine (sCr) levels >353.6 um/L prior to the initiation of ECMO, or for incomplete data. The Ethics Committee of Shanghai Chest Hospital approved this study with a waiver of informed consent because this observational investigation did not modify the existing diagnosis or therapeutic strategies and did not contain any identifiable patient information.

ECMO management

ECMO for circulatory support was provided to patients with one or more of the following indicators, after large doses of vasoactive drugs and an intra-aortic balloon pump were already administered: cardiac index <1.8 L/min/m^2, left atrioventricular pressure or pulmonary artery wedge pressure >20 mmHg, arterial systolic pressure <90 mmHg or average pressure <60 mmHg, urine output <20 mL/h (in adults with normal renal function), the presence of metabolic acidosis, and systemic circulatory resistance >2100 dyn/sec/cm^5. ECMO for respiratory support was given to patients with reversible respiratory failure whose Murray score was >3 or pH was <7.20.

The Medtronic ECMO package (Medtronic, Minneapolis, MN, USA) with Carmeda coating was used prior to 2008. After January 2008, the ECMO system included the Maquet oxygenator (Maquet, Hirrlingen, Germany) with PLS Bioline coating and Medtronic Biopump and tubing without bio-coating. After January 2009, the Maquet ECMO package (Maquet) became available and remained the only choice for disposable ECMO to date. The priming strategy-aimed to maintain homeostasis or prevent homeostasis disturbances-varied according to patient weight, hemoglobin and electrolyte levels.

Cannula sites for VA-ECMO were the femoral artery and femoral vein. VV-ECMO withdrew blood from the inferior vena cava through a femoral venous cannula, and supplied oxygenated blood back to the patient through the internal jugular vein. Anticoagulation was achieved by unfractionated heparin to maintain the activated clotting time (ACT) between 180 and 220 s. If bleeding was difficult to control, the ACT was permitted to be kept between 130 and 150 s for 24 h. Platelet levels were maintained above 60 × 10^9/L. The mechanical ventilation strategy followed the protective ventilation principle with an inflation maneuver at an interval of 4-6 h.

Data collection and definitions

The following demographic and clinical data was collected: age, gender, comorbidconditions, indications for ECMO, ECMO configuration, vasoactive inotrope score (VIS) [16] prior to ECMO initiation (dopamine [μg/kg/min] + dobutamine [μg/kg/min] + 100 × epinephrine [μg/kg/min] + 10 × milrinone (μg/kg/min) + 10000 × vasopressin [U/kg/min] + 100 × norepinephrine [μg/kg/min]), duration of ECMO, length of intensive care unit (ICU) stay, and in-hospital mortality. Clinical and laboratory data collected included: occurrence of infection, occurrence of massive bleeding, disseminated intravascular coagulation, total red blood cell (RBC) transfusion, maximum plasma free hemoglobin (FHb) level, and maximum serum creatinine (sCr) values.

AKI was defined using Acute Kidney Injury Network (AKIN) criteria (daily urine output ≤0.5 mL/kg/h for 6 h and/or an increase in sCr ≥0.3 mg/dL or >1.5 times increase within 48 h) [9]. Patients were categorized into two groups (AKI or no-AKI). Nosocomial infection was defined as an infection that occurred 24 h after ECMO initiation and 48 h before termination with positive blood cultures. Massive bleeding was defined as a transfusion requirement of more than 10 units of blood in 24 h, or greater than 4 units in 1 h.

Statistical analysis

All analyses were performed using SPSS statistical software (version 13, SPSS Inc., Chicago, IL, USA). Values were expressed as the mean ± standard deviation for continuous variables. Differences were analyzed by the t-test for continuous variables and the chi-squared test for categorical variables. For the multivariate analysis, Cox-proportional hazard regression analysis for in-hospital mortality or AKI was performed. A *p*-value of <0.05 was considered statically significant.

Results

The study cohort included 71 patients with a mean age of 48.4±17.2 years; 44 (62.0%) were male. The indications for ECMO included car-

Table 1. Patient characteristics according to survival status (Demographic data and clinical characteristics of hospital survivors and non-survivors)

	Survivor (n=32)	Non-survivor (n=39)	P
Age (years)	46.2±17.5	50.2±17.0	0.338
Male sex	22/32	22/39	0.287
Causes of ECMO support			
ARDS	15/32	11/39	0.104
Non-ARDS lung causes	5/32	4/39	0.499
Post-cardiotomy	7/32	11/39	0.542
Non-operative cardiac causes	4/32	9/39	0.252
Others	1/32	4/39	0.243
VA configuration	16/32	30/39	0.018
Vasoactive inotropic score before ECMO initiation	13.4±6.4	15.3±6.3	0.195
Duration of ECMO (days)	13.9±20.1	14.2±6.5	0.920
Lenth of ICU stay (days)	18.0±7.3	24.3±10.9	0.007
No-AKI	12/32	7/39	0.064
Infection	14/32	22/39	0.344
MasssiveBleeding	8/32	16/39	0.209
DIC	5/32	9/39	0.553
Total RBC transfusion (U)	15.2±9.7	16.1±7.1	0.658
Max FHb (g/L)	0.55±1.2	0.44±0.27	0.589
Max sCr (umol/L)	172.8±71.6	184.0±56.4	0.460

Difference was analyzed by t-test in continuous variables and chi-square test in categorical variables. ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; VA, venoartierial; ICU, intensive care unit; AKI, acute kidney injury; DIC, disseminated intravascular coagulation; RBC, red blood cell; FHb, free hemoglobin; sCr, serum creatinine.

Table 2. Multivariate Cox-proportional hazard regression analysis for in-hospital mortality

	Hazard ratio (95% CI)	B	P
Age (≤60 vs. >60)	1.700 (0.719-4.016)	0.530	0.227
Male sex (male vs. female)	1.384 (0.617-3.103)	0.325	0.430
Causes of ECMO support (vs. ARDS)			0.154
Non-ARDS lung causes	0.337 (0.073-1.564)	-1.086	0.165
Post-cardiotomy	0.336 (0.082-1.381)	-1.091	0.130
Non-operative cardiac causes	0.710 (0.166-3.032)	-0.343	0.644
Others	1.712 (0.315-9.300)	0.538	0.533
VA configuration (VA vs. VV)	0.212 (0.054-0.836)	-1.553	0.027
Vasoactive inotropic score before ECMO initiation	1.580 (0.579-4.309)	0.457	0.372
lenth of ICU stay (days) (≤20 vs. >20)	0.192 (0.069-0.537)	-1.649	0.002
no-AKI (vs. non-AKI)	1.465 (0.301-7.121)	0.382	0.636
Infection	1.890 (0.851-4.198)	0.636	0.118
Masssive Bleeding	1.220 (0.359-4.142)	0.199	0.750
DIC (vs. no)	0.864 (0.219-3.411)	-0.147	0.834
Total RBC transfusion (U) (≤20 vs. >20)	0.976 (0.358-2.661)	-0.025	0.961
Max FHb (g/L) (≤0.5 vs. >0.5)	0.594 (0.228-1.552)	-0.520	0.288
Max sCr (umol/L) (≤150 vs. >150)	0.500 (0.143-1.749)	-0.693	0.278

All above variables were inputted in multivariate Cox-proportional hazard regression analysis. ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; VA, venoartierial; ICU, intensive care unit; AKI, acute kidney injury; DIC, disseminated intravascular coagulation; RBC, red blood cell; FHb, free hemoglobin; sCr, serum creatinine.

diovascular acute respiratory distress syndrome (ARDS) (26, 36.6%), non-ARDS lung disease (9, 12.7%), post-cardiotomy (18, 25.4%), non-operative cardiac causes (13, 18.3%), and oth-

Table 3. Univariate analysis for AKI

	No-AKI (n=19)	AKI (n=52)	P
Age (years)	48.8±18.5	48.2±16.9	0.901
Male sex	13/19	31/52	0.587
Causes of ECMO support			
ARDS	5/19	21/52	0.405
Non-ARDS lung causes	4/19	5/52	0.236
Post-cardiotomy	3/19	15/52	0.362
Non-operative cardiac causes	5/19	8/52	0.313
Others	2/19	3/52	0.605
VA configuration	11/19	35/52	0.576
Vasoactive inotropic score before ECMO initiation	15.4±6.7	14.1±6.3	0.436
Duration of ECMO (days)	10±4.4	15.6±16.3	0.142
Lenth of ICU stay (days)	16.4±7.1	23.3±10.2	0.009
Hospital mortality	7/19	32/52	0.105
Infection	9/19	27/52	0.793
Masssive bleeding	8/19	16/52	0.405
DIC	3/19	11/52	0.745
Total RBC transfusion (U)	8±2.3	18.5±8	0.000
Max FHb (g/L)	0.77±1.54	0.38±0.26	0.079
Max sCr (umol/L)	132.4±23.4	196.0±65.1	0.000

Difference in univariate analysis wascalculated by t-test in continuous variables and chi-square test in categorical variables. ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; VA, venoartierial; ICU, intensive care unit; AKI, acute kidney injury; DIC, disseminated intravascular coagulation; RBC, red blood cell; FHb, free hemoglobin; sCr, serum creatinine.

Table 4. Multivariate Cox-propotional hazard regression analysis for AKI

	Hazard ratio (95% CI)	B	P
Age (≤60 vs. >60)	1.046 (0.463-2.360)	0.045	0.914
Male sex (male vs. female)	0.890 (0.400-1.981)	-0.117	0.775
VA configuration (VA vs. VV)	0.311 (0.111-0.877)	-1.166	0.027
Vasoactive inotropic score before ECMO initiation (≤20 vs. >20)	1.152 (0.468-2.837)	0.142	0.758
Lenth of ICU stay(days) (≤20 vs. >20)	0.327 (0.145-0.737)	-1.117	0.007
Hospital mortality	0.690 (0.320-1.489)	-0.371	0.344
Infection (vs. no)	2.280 (1.065-4.878)	0.824	0.034
Masssive bleeding (vs. no)	0.707 (0.202-2.479)	-0.347	0.588
DIC (vs. no)	1.284 (0.329-5.013)	0.250	0.719
Total RBC transfusion (U) (≤20 vs. >20)	1.426 (0.671-3.031)	0.355	0.357
Max FHb (g/L) (≤0.5 vs. >0.5)	0.734 (0.311-1.729)	-0.310	0.479
Max sCr (umol/L) (≤150 vs. >150)	1.431 (0.589-3.475)	0.358	0.429

All above variables were inputted in multivariate Cox-proportional hazard regression analysis. ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; VA, venoartierial; ICU, intensive care unit; AKI, acute kidney injury; DIC, disseminated intravascular coagulation; RBC, red blood cell; FHb, free hemoglobin; sCr, serum creatinine.

ers (5, 7%). VA ECMO support was performed in 46 (64.8%) patients and VV in 25 (35.2%). The median duration of ECMO (from initiation to weaning) was 12 (3-122) days. The length of ICU stay was 21.4±9.9 days. Thirty-two (45.1%) patients survived to hospital discharge. Fifty-two (73.2%) developed AKI.

First, factors associated with in-hospital mortality were explored. Among various factors, ECMO configuration was significantly associated with mortality, with more VA mode configurations in the non-survivor group (30/39 vs. 16/32, $p<0.05$). Length of ICU stay was significantly shorter in the survivor group (18.0±7.3

vs. 24.3±1.9, p<0.05). Although AKI developed less frequently in survivors (7/39 vs. 12/32, p= 0.064), this difference did not reach statistical significance (**Table 1**). We performed a multivariate Cox-proportional hazard analysis to adjust for confounding effects among the selected variables. VA configuration (OR, 0.212; 95% CI, 0.054-0.836; p<0.05) and length of ICU stay (OR, 0.192; 95% CI, 0.069-0.537; p<0.05) were significantly associated with increased in-hospital mortality (**Table 2**).

Then, characteristics between patients with and without AKI were compared. Patients who developed AKI had longer ICU stays (23.3±10.2 vs. 16.4±7.1, p<0.05) and received more blood transfusions (18.5±8 vs. 8±2.3, p<0.05) compared with patients without AKI. Maximum sCr levels during ECMO were significantly higher in AKI patients (196.0±65.1 vs. 132.4±23.4, p< 0.05; **Table 3**). In the multivariate logistic regression analysis, VA configuration (OR, 0.311; 95% CI, 0.111-0.877; p<0.05), length of ICU stay (OR, 0.327; 95% CI, 0.145-0.737; p<0.05) and infection (OR, 2.280; 95% CI, 1.065-4.878; p<0.05)were found to be significant risk factors for the development of AKI (**Table 4**).

Discussion

AKI is frequently observed during ECMO support. Several studies report a high incidence of AKI in patients supported with ECMO, with a reported 4-fold increase in mortality [4]. Unfortunately, the pathophysiologic mechanisms of kidney injury during ECMO remain poorly understood. Although initiation of ECMO can lead to restitution of physiology, which may prevent the progression of preexisting disease or minimize harm caused by salvage treatment (i.e. inotropic agents), it may also contribute to kidney dysfunction through other mechanisms [17, 18]. In this study, we investigated the risk factors for AKI and in-hospital mortality in patients receiving ECMO support. Although similar research has been performed recently [8, 9, 19, 20], the incidence of AKI during ECMO and its impact on outcomes is extremely variable and depends on the definitions applied to classify renal failure, the indications for ECMO, and the studied population [9, 21]. Therefore, we conducted this retrospective study to determine the risk factors for AKI and in-hospital mortality in ECMO patients in our single center.

We demonstrated that patients on VA-ECMO had higher in-hospital mortality rates than those on VV mode, and that the VA mode was a risk factor for death. While VV-ECMO supports respiratory function exclusively, VA-ECMO supports circulatory and respiratory function. Thus, patients on VA-ECMO tended to be in a more critical condition. This was consistent with studies of Lee et al. [19]. Among various factors, length of ICU stay was associated with in-hospital mortality, which is understandable. Unlike previous studies, this study showed no significant differences in mortality among patients with AKI and those without AKI during ECMO therapy. This result was not exclusive to this study alone [9], but increases the complexity of the relationship between AKI and ECMO outcomes, and confirmed what was previously mentioned; that the study results might depend on the patient population. As a result, additional studies with larger sample sizes are required.

We also explored the risk factors for AKI during ECMO. AKI patients had longer ICU stays, higher blood transfusion requirements, and higher sCr levels. VA mode, length of ICU stay, and infection were the risk factors for AKI. Maximum FHb levels were among the explored factors, because hemolysis has been previously reported to be associated with AKI [22]. Lou et al. found that hemolysis was associated with adverse outcomes in pediatric patients receiving ECMO [20]. The explanation for our results are not definitely clear, but may be due to the fact that we measured FHb daily; and a FHb level seldom exceeded 1.0 g/L before the ECMO disposable was changed. The impact of vasoactive agents on AKI was also explored. Antonucci et al. found in a retrospective study that the development of AKI was associated with the severity of disease, initial lactate levels, the use of inotropic agents, and VA-ECMO [9]. However, this study did not demonstrate vasoactive agents, as assessed by VIS, to be a risk factor of death or AKI.

The present study has several limitations. First, it is a retrospective study performed in a small cohort of patients at a single center. Future studies with larger sample sizes would provide greater certainty in the findings. Second, we did not explore the association between continuous renal replacement therapy (CRRT) and mortality, as the indication for CRRT usage underwent several changes during recent years in our

institute; we believe that this might have resulted in bias. Third, we did not study the role of potentially nephrotoxic agents during ECMO support because we could not ensure prescriptions would be collected without omitting the medical record of early years. Finally, long-term survival analysis and quality-of-life evaluation were not performed as some of the follow-up data was unusable.

In conclusion, AKI was common in adult patients receiving ECMO support but not shown to be a risk factor for in-hospital mortality. VA-ECMO mode and length of ICU stay were associated with in-hospital mortality. VA-ECMO mode, length of ICU stay, blood transfusion, sCr levels, and infection were significantly related to AKI occurrence.

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Disclosure of conflict of interest

None.

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