Original Article

Retrospective study on the effects of the prognosis of patients treated with extracorporeal membrane oxygenation combined with continuous renal replacement therapy

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Background: Patients undergoing extracorporeal membrane oxygenation (ECMO) treatment often have severe fluid overload and electrolyte imbalances and may even suffer acute kidney injury (AKI). It is often necessary to use continuous renal replacement therapy (CRRT). In this study, we aimed to retrospectively analyze the prognosis of patients treated with ECMO combined with CRRT and to find the independent factors that affect the survival rate.

Methods: There were 32 patients who were treated with ECMO combined with CRRT in our hospital from January 2007 to December 2017 who were analyzed. All of the patients were divided into a survival group and death group. The clinical indicators and biochemical indexes of the two groups were observed, and their differences were compared. Multivariate logistic regression analysis was carried out to determine the independent risk factors.

Results: The fluid balance at ECMO day 3, SOFA score and lactate at CRRT initiation, sequential organ failure assessment (SOFA) score at ECMO weaning, CRRT duration, ECMO to CRRT interval, mechanical ventilation (MV) duration, length of ICU, and overall hospital length of stay were statistically significant ($P<0.05$). The clinical biochemical indexes at CRRT initiation and ECMO weaning [serum creatinine, pH, white blood cell (WBC), hemoglobin (Hb), bilirubin]; patient's age, gender and BMI; and the fluid balance at ECMO days 1 and 7 were not statistically significance ($P>0.05$). The fluid balance at ECMO day 3 and lactate at CRRT initiation by multivariable logistic regression analysis were independent risk factors affecting patient prognosis.

Conclusions: The fluid balance at ECMO day 3 and lactate at CRRT initiation are the prognosis independent risk factors for ECMO + CRRT patients.

Keywords: Extracorporeal membrane oxygenation (ECMO); continuous renal replacement therapy (CRRT); prognosis

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Introduction

In recent years, the number of patients with life-threatening heart or lung failure treated with extracorporeal membrane oxygenation (ECMO) has been increasing. About 30–50% of patients with ECMO have acute kidney injury (AKI). Although continuous renal replacement therapy (CRRT) provides an effective treatment, studies have found that the 98-day survival rate of ECMO patients with AKI is only 17% (1). CRRT using during ECMO is an independent risk factor related to ECMO weaning failure (2) and the prediction (3). The indication of ECMO and CRRT combination has not been clearly defined. Most studies are based on pediatric data, and adult data are insufficient. Moreover, ECMO patients are in a critical condition, and some patients are not up to the KDIGO classification standards for AKI (for example, their SCr value may not up to the standard, or the oliguria time was <6 h), but they have serious electrolyte, acid-base balance disorder and excessive water load, so early administration of CRRT are given for them. The effect of this early administration of CRRT in ECMO patients has not been studied. We here conducted a retrospective analysis of ECMO patients treated by the ECMO team in our hospital, and we preliminarily evaluated the significance of CRRT in the treatment of ECMO patients.

Methods

General information

Thirty-two patients who underwent ECMO + CRRT treatment in our hospital from January 2007 to December 2017 were analyzed. There were 22 cases who were male and 10 cases who were female ranging in age from 16 to 69 years. According to the situation at the time of discharge, the patients were divided into the survival group (13 cases) and the death group (19 cases) (*Table 1*).

Table 1 Diagnosis of primary diseases in patients with ECMO + CRRT

Primary disease	Number of patient cases (n=32)
Valve implantation	8
CABG	3
Pericarditis	2
Congenital heart disease	2
Viral myocarditis/stress heart disease	7
AMI	6
Sepsis	4

ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; CABG, coronary artery bypass graft; AMI, acute myocardial infarction.

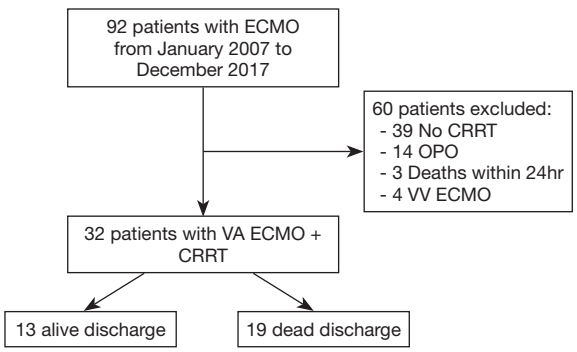

Figure 1 Outcomes of patients with ECMO combined CRRT. ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; OPO, Organ Procurement Organizations.

Inclusion and exclusion criteria

Inclusion criteria

Patients who received CRRT + ECMO treatment were included. And the indicators for using CRRT were: (I) increase in SCr of 1.5–1.9 times baseline; OR increase in sSCr of ≥0.3 mg/dL (≥26.5 μmol/L); OR urine output <0.5 mL/kg/h for 6–12 h [KDIGO standard established by AKI in 2012 (4)]. (II) ECMO patients who had significant fluid overload; severe hyperkalemia hypernatremia, or both; other serious electrolyte disturbances; and severe acid-base balance disorders that could not be easily corrected.

Exclusion criteria

(I) Patients who did not receive CRRT. (II) ECMO patients with organ procurement organization (OPO). (III) Patients who died within 24 h of CRRT (*Figure 1*).

CRRT and ECMO connection

ECMO centrifugal pumps and membrane were from Maquet (Fairfield, NJ, USA). The CRRT was performed using a Prismaflex machine (Gambro, Lund, Sweden).

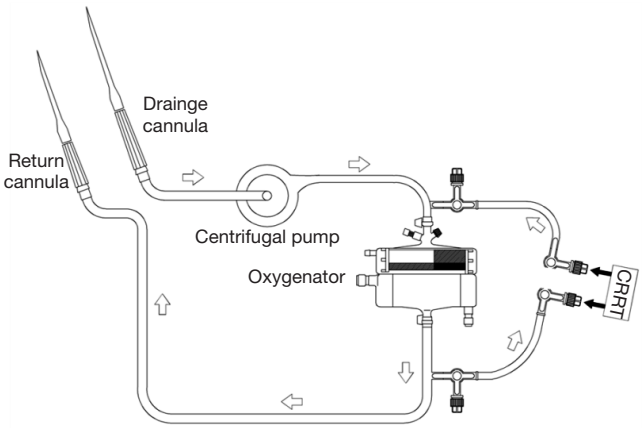

Figure 2 Diagram of ECMO connecting CRRT. ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy.

The connection between CRRT and ECMO is shown in *Figure 2* (5). CRRT usually involves CVVH mode, while some patients were given CVVDH mode. The replacement solution was prepared using Port formula. The pre-dilution method maintained the blood flow rate at 150–250 mL/h according to the patient's circulation, and the replacement rate was generally 1.5–2.5 L/h. Body fluid ultrafiltration rate can be adjusted according to the patient's hemodynamics.

Observation parameters

Statistical analysis was performed on the data of all patients during hospitalization. The gender, age, BMI, ECMO duration, CRRT duration, mechanical ventilation (MV) duration, ICU and hospital length of stay were observed. The fluid balance at ECMO days 1, 3 and 7, clinical biochemical indexes [creatinine, pH, sequential organ failure assessment (SOFA) scores, white blood cell (WBC), bilirubin, and lactate] at CRRT initiation and ECMO weaning in both survival and death groups were also determined.

Statistical analysis

SPSS 22.0 statistical software was used for statistical analysis. Data were expressed as the frequency and percentage for categorical variables and the mean ± standard deviation (SD) for continuous variables. The values are presented as the mean ± SD and the median and inter quartile range (IQR). All demographic data, clinical data and laboratory findings (non-normally distributed variables) were compared between the two groups (survivors and non-survivors) using the Wilcoxon signed rank test and Mann-Whitney U test for other variables. To compare the proportions of patients, χ^2 test or Fisher exact test was performed. Multivariate logistic regression analysis was performed to analyze multiple factors. All statistical tests were two-sided and significance was defined as $P<0.05$.

Results

Comparison of clinical data between survival and death groups

CRRT duration, ECMO to CRRT interval, MV duration, ICU and hospital length were statistically significant between the two groups (all $P<0.05$). There was not statistically significant in other factors (all $P>0.05$) between the two groups (*Table 2*).

Comparison of clinical biochemical indexes affecting patients' survival

The fluid balance at ECMO day 3, SOFA score and lactate at CRRT initiation, SOFA score at ECMO weaning were statistically significant between the survival and death groups (all $P<0.05$). The fluid balance at ECMO days 1 and 7, the clinical biochemical indexes (serum creatinine, pH, WBC, Hb, bilirubin) at CRRT initiation and ECMO weaning were not statistically significant between the two groups (all $P>0.05$) (*Table 3*).

Multivariate logistic regression analysis

We performed a multivariable logistic regression analysis of risk to the prognosis of patients with variables including lactate/SOFA score at CRRT initiation and fluid balance at ECMO day 3. The lactate at CRRT initiation (OR 2.115, 95% CI: 1.102–4.058, P=0.024) and fluid balance at ECMO day 3 (OR 5.268, 95% CI: 1.381–20.088, P=0.015) were the independent risk factors to the prognosis of patients.

Discussion

Patients with severe cardiogenic shock often experience systemic inflammatory reactions and persistent vasospasm and coagulopathy due to low cardiac output or hypoxemia lasting hours or even days prior to ECMO treatment.

Table 2 Comparison of clinical data between survival and death groups ($\bar{x}$±s)

Factors	Survival group (n=13)	Death group (n=19)	P value
Number of male (male, %)	8 (61.54)	14 (73.68)	0.483
Age	48.00±14.11	54.84±6.46	0.073
BMI	21.34±1.21	22.16±1.97	0.189
ECMO duration (h)	145.23±20.33	171.74±45.17	0.057
CRRT duration (h)	114.69±27.03	148.37±48.96	0.032
ECMO to CRRT interval (h)	5.38±4.31	10.37±8.39	0.036
Mechanical ventilation duration (days)	8.62±1.76	11.05±2.80	0.009
ICU length of stay (days)	10.54±1.61	15.84±2.93	0.000
Hospital length of stay (days)	22.77±3.54	16.74±3.38	0.000

Values are presented as median (range) or mean ± standard deviation (SD). BMI, body mass index.

Table 3 Comparison of clinical biochemical indexes affecting patients' survival

Fluid balance and biochemical indexes	Survival group (n=13)	Death group (n=19)	P value
Fluid balance at ECMO day 1	1,307 (1,077–1,600)	1,296 (990–1,568)	0.878
Fluid balance at ECMO day 3	210 (–125 to 625)	1,090 (750–1,590)	0.000
Fluid balance at ECMO day 7	342 (360–1,175)	193 (–100 to 400)	0.773
Serum creatinine at CRRT initiation	137.31±51.75	169.89±50.23	0.085
pH at CRRT initiation	7.24±0.12	7.16±0.13	0.103
SOFA score at CRRT initiation	12.31±1.93	15.31±2.36	0.001
WBC at CRRT initiation ($\times10^9$/L)	12.32±2.05	12.49±2.20	0.823
Hb at CRRT initiation (g/L)	102.23±11.63	97.00±8.78	0.157
Bilirubin at CRRT initiation (mmol/L)	52.77±21.43	56.42±30.79	0.714
Lactate at CRRT initiation (mmol/L)	4.66±2.54	7.07±1.66	0.003
Serum creatinine at ECMO weaning	190.87±73.08	206.58±80.73	0.578
pH at ECMO weaning	7.44±0.07	7.42±0.06	0.365
SOFA score at ECMO weaning	8.62±0.77	18.68±1.38	0.000
WBC at ECMO weaning ($\times10^9$/L)	11.89±2.67	12.99±2.24	0.213
Hb at ECMO weaning (g/L)	103.23±9.67	99.37±8.66	0.247
Bilirubin at ECMO weaning (mmol/L)	48.77±23.54	67.21±41.51	0.125
Lactate at ECMO weaning (mmol/L)	1.62±0.54	2.95±1.31	0.002

Values are presented as median (range) or mean ± standard deviation (SD). CRRT, continuous renal replacement therapy; SOFA, sequential organ failure assessment; WBC, white blood cell; Hb, hemoglobin.

Both of these factors may lead to multiple organ failure (MOF) (6). Studies have shown that among patients receiving ECMO, more than 30% have AKI (7), and the prognosis is worse than in those without renal failure. For this reason, clinical cases of ECMO often require combined treatment with CRRT. Schmidt *et al.* recently found that 60% of the 172 adult patients who underwent ECMO were on CRRT, and ECMO combined with CRRT

Table 4 Multivariate logistic regression analysis of factors affecting patients' survival rate

Variable	OR (95% CI)	P value
Fluid balance at ECMO day 3	5.268 (1.381–20.088)	0.015
Lactate at CRRT initiation	2.115 (1.102–4.058)	0.024
Constant	0.001	0.014

ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy.

was an independent predictor of 90-day mortality (8). Three studies (9-11) found that hospital mortality was significantly higher in ECMO + CRRT patients than in ECMO alone (OR 5.89, 95% CI: 4.38–7.92, P<0.00001). Even after matching the patient's age, weight, diagnosis, and ECMO patterns, the OR was 6.82 (95% CI: 4.97–9.36, P<0.00001) (12). However, there are few studies on the specific factors that affect the mortality of these patients.

Fluid overload is associated with mortality, oxygenation, MV and duration of ICU in critically ill patients. Patients with ECMO are particularly prone to fluid overload, and fluid balance management is often a problem that needs to be addressed (13). In critically ill patients with ECMO, fluid overload leads to worse prognosis (14). Our data also demonstrate that fluid overload at ECMO days 3 and 7 were both higher in non-survivors (*Table 3*). Radiolabeled isotopes show that the fluid overload is mainly diffusely distributed throughout the total body water and extracellular fluids space during ECMO (15). Continuous accumulation of fluid overload that cannot be cleared increases mortality rate (16) and prolongs ECMO duration (12). These findings are consistent with those of our study (*Tables 2* and *3*). Fluid overload may reflect the severity of illness. Correction of fluid overload can improve lung function and reduce ECMO weaning time (17). In particular, the incidence of fluid overload in neonatal and child ECMO is higher (18). Gbadegesin *et al.* reported that the fluid balance in patients with ECMO survivors was lower than that in the death group (19). Symons *et al.* found that the use of CRRT in ECMO can allow more precise fluid management, which may help reduce the ECMO duration (20). The International ELSO Guidelines recommend 'recovering the extracellular fluid volume to normal (dry weight) and maintaining it' (21). These studies indicate that early CRRT prevention of fluid overload may reduce mortality and improve patient outcome. After adjusting for other significant confounding variables (fluid balance at ECMO day 1, SOFA score at CRRT initiation, lactate at CRRT initiation, SOFA score at ECMO weaning, lactate at ECMO weaning) using logistic regression analysis, an increase in fluid overload on day 3 was found to be an independent predictor of discharge death (*Table 4*). The increase in fluid volume in the death group at ECMO day 3 may suggest an irreversible decrease in cardiac function or the progressive failure of microcirculation. We have calculated the ECMO to CRRT interval time, and found it to be significantly shorter in the survival group (*Table 2*). These results suggested that we should use CRRT early, reverse fluid overload, and improve cardiac function.

This study further found that lactate at CRRT initiation in the survival group was significantly lower than that in the death group. Peigh *et al.* found in a retrospective analysis of 73 patients with VA-ECMO that lactate to be an independent risk factor for the prognosis of patients with ECMO (22). Cheng *et al.* (23) found that in 145 ECMO patients with or without sepsis, lactate in patients who died at hospital was significantly higher than that of 71 survivors. In 94 patients with pure cardiac VA ECMO, lactate in 1-year survivors was significantly lower than in those who died (8.6 *vs.* 2.4 mEq/L, P≤0.034) (24). This study also found that lactate at CRRT initiation to be an independent risk factor that affected the patient's survival rate. This suggests that microcirculatory perfusion has an impact on mortality. Fluid overload can lead directly to cellular edema and microcirculatory disturbances, which also suggests that early use of CRRT may benefit patients.

While the present study has supplied useful information about ECMO-treated patients, it has several limitations that must be acknowledged. We have included all patients who meet the inclusion and exclusion criteria during the study period for analysis. However, the small patient population and the retrospective nature of the study do not allow us to draw any conclusion about the effectiveness of combined ECMO-CRRT treatment. According to the clinical control test (the test level is 0.05), the accuracy of this study was 80%. Larger series from multi-center RCT experiments are needed to confirm the effectiveness of the study and to provide a reliable theoretical basis for follow-up clinical work.

In summary, our results suggest that lactate at CRRT initiation and fluid balance at ECMO day 3 are the independent risk factors of prognosis for patients on ECMO. The main indicator of evaluation was fluid balance at ECMO day 3, which were 210 and 1,090 mL in the death and survival groups. If CRRT device is introduced as soon

as possible into the ECMO circuit, it may be possible to promote early fluid balance and improve patient survival.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Ethical Committee of Southwest Hospital (the number/ID of the approval is KY 201847).

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