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ORIGINAL RESEARCH

Predictors for Successful Weaning from Veno-Venous Extracorporeal Membrane Oxygenation in Patients with Severe Acute Respiratory Distress Syndrome

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Purpose: This study aimed to investigate the predictors of successful weaning from veno-venous extracorporeal membrane oxygenation (VV-ECMO) among patients with severe acute respiratory distress syndrome (ARDS) in our centre.

Methods: The clinical data of patients with severe ARDS who were treated with VV-ECMO between January 2019 and January 2022 were retrospectively analysed. Due to the outcomes of weaning from extracorporeal membrane oxygenation (ECMO), the considered patients with ARDS were divided into a successful weaning group and an unsuccessful weaning group. Logistic regression analysis was employed to evaluate predictors for successful VV-ECMO weaning among patients with severe ARDS.

Results: A total of 65 patients with severe ARDS were included for analysis. Among them, 31 (47.69%) patients were grouped into the successful weaning group, while 34 (52.30%) patients were grouped into the unsuccessful weaning group. Univariate analysis showed that Age (odds ratio [OR] =0.939; 95% confidence interval [CI] =0.896–0.983; $p = 0.008$), APACHEII scores before ECMO (OR =0.651; 95% CI =0.537–0.789; $p < 0.001$), Renal insufficiency (OR =0.061; 95% CI =0.012 −0.298; $p = 0.001$), MAP before ECMO (OR =1.246; 95% CI =1.114–1.392; $p<0.001$), PaO2 during ECMO (OR =1.083; 95% CI =1.033–1.135; $p = 0.001$), and CRRT (OR =0.080; 95% CI =0.022–0.285; $p = 0.008$) were identified as an independent predictor of successful VV-ECMO weaning. After multivariate analysis was performed, APACHE II scores before ECMO (OR = 0.651; 95% CI = 0.462–0.919; $p = 0.015$) were identified as independent predictors for successful VV-ECMO weaning.

Conclusion: In conclusion, in severe ARDS patients, lower APACHE II scores predicted successful wean from VV-ECMO.

Keywords: acute respiratory distress syndrome, extracorporeal membrane oxygenation, predictor, weaning, acute physiology and chronic health evaluation II

Introduction

Acute respiratory distress syndrome (ARDS) is a severe clinical syndrome that is usually characterised by severe lung injury and can endanger the patient's life.[1] According to clinical data statistics, the fatality rate of severe ARDS is as high as 40%.[1]

Currently, extracorporeal membrane oxygenation (ECMO) is a commonly used means in the treatment of ARDS.[2] The technique can act as an alternative organ of the lung and function to remove carbon dioxide from the body.[3] When patients develop ARDS, ECMO can exercise lung function, thereby slowing lung injury.[4] Extracorporeal membrane oxygenation can be further divided into veno-arterial (VA)-ECMO and veno-venous (VV)-ECMO). The proportion of VV-ECMO use in ARDS patients has gradually increased.[5] Combes et al found that ECMO use in patients with severe ARDS did not have a significantly lower mortality rate than conventional mechanical ventilation.[6] Similarly, Peek et al reported that an ECMO-based management protocol could significantly improve the survival of severe ARDS with

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improved cost-effectiveness compared with other techniques, including mechanical ventilation.[7] With technological advancements in extracorporeal ventilation techniques, ECMO is applied increasingly for severe ARDS.

However, in patients with persistent lung injury, weaning from ECMO can be challenging. The ideal process to wean a patient off ECMO organ support starts once the lung function has sufficiently recovered.[8] Identifying the predictors for weaning outcomes is associated with the improvement of the outcome of ECMO support.[9] However, the factors to predict successful weaning from ECMO are less well understood. Only a few studies that focus on ECMO weaning predictors are available. For instance, Lee et al[10] reported that high platelet counts played a key role in the successful weaning off ECMO. In this study, we aim to investigate the predictors of successful weaning from ECMO among patients with severe ARDS.

Methods

Patients

This study was a retrospective analysis, and the study was approved by the Ethics Committee of First Affiliated Hospital of Gannan Medical College of Jiangxi Province. The diagnostic criteria for ARDS were performed according to the Berlin definition.[11] Inclusion criteria: (1) patients with severe ARDS were defined as having a positive end-expiratory pressure (PEEP) ≥5 mmHg and an arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio ≤100 mmHg; (2) the ECMO treatment was started within 7 days after ventilation.[12] Patients aged <18 years were excluded from the study.

When a ventilator is used to assist patient respiration, it is necessary to adjust the respiration rate carefully according to the clearance condition of carbon dioxide, but the adjustment range may not exceed other preset parameters. The ventilator must have a resting setting that meets at least the following criteria: plateau pressure ≤25 cm H_2O or inspiratory pressure ≤15 cm H_2O and PEEP ≥10 cm H_2O. In VV-ECMO, the goal of ventilation optimisation is to achieve ultra-protective ventilation; for patients using VV-ECMO, a respiratory rate of 10 breaths/minute, inspiratory pressure 10 cm H_2O, PEEP 10 cm H_2O and FiO_2 40% should be maintained. During VV-ECMO therapy, if the patient's oxygenation and carbon dioxide removal goals are not met, priority should be given to adjusting the settings of the ECMO circuit rather than simply increasing the ventilator's parameters. This approach helps ensure that the patient receives ventilatory support that best suits their current condition.

To begin, the flow rate of ECMO was set at 3.0–3.5 L/min to help the patient recover peripheral circulation. All patients started ECMO therapy in the catheterisation laboratory, and the initial flow rate and rotation speed were set appropriately. As treatment progressed, physicians adjusted ECMO flow rates based on multiple indicators of peripheral circulatory failure, including arterial blood gas analysis results, mixed venous oxygen saturation, lactate levels and urine output. The flow rate of ECMO was progressively decreased if these measures showed an improvement in the patient's circulatory status. When the flow rate of ECMO dropped to 1.0 L/min and the patient's vital signs and the above circulatory collapse indicators were within acceptable ranges, this indicated that ECMO therapy could be stopped and the patient weaned off ECMO equipment. This process requires close monitoring of the patient's condition to ensure a safe and smooth transition.

Successful weaning from VV-ECMO was defined as (1) the ECMO flow was reduced to 1–1.5 L/min and maintained at this flow for >2 hours, ensuring that the patient maintained adequate oxygenation while ventilatory reserves were assessed. Patients could tolerate low ECMO airflow (< 2 L/min), and monitoring was continued for at least 4–6 hours to ensure that the patient could maintain adequate oxygenation and carbon dioxide removal, and (2) the patient survived >48 hours after ECMO removal.[9,13] Based on the outcomes of weaning from ECMO, the considered ARDS patients were divided into a successful weaning group and an unsuccessful weaning group.

Data Collection

The following information on each patient was retrospectively analysed: demographic data; Acute Physiology and Chronic Health Evaluation II (APACHE II) scores before ECMO; mechanical ventilation time; ECMO duration; ventilator settings before ECMO organ support, such as tidal volume, PEEP, mean arterial pressure (MAP) and PaO_2

/FiO_2; lactate levels before ECMO; left ventricular ejection fraction before ECMO; lactate levels during ECMO; PaO_2 during ECMO; use of continuous renal replacement therapy (CRRT) during ECMO; the existence of ventilator-associated pneumonia; and application of VA-ECMO. The patient's data during ECMO organ support (lactate levels and PaO_2) was extracted using the average value.

Statistical Methods

The SPSS (version 22.0) software package (IBM SPSS, NY, USA) was used for data analysis. The chi-squared test or Fisher's exact test was used for categorical data comparison, and the *t*-test was used for normally distributed quantitative data comparison. Logistic regression analysis with 95% CIs and ORs was used to evaluate independent predictors. The correlation between each independent variable and the outcome variable was assessed through univariate analysis (such as the chi-squared test or *t*-test). Only variables that were significantly associated with the outcome variable (a *p*-value of <0.05) were retained in multivariate logistic regression analysis.

Results

A total of 65 patients, with a mean age of (48.72 ± 11.71) years, were included for analysis. Among them, 31 (47.69%) patients (26 men and 5 women) were successfully weaned from ECMO; they formed the successful weaning group. Twenty-eight of the 31 patients (90.32%) in the successful weaning group survived to hospital discharge; 2 patients (6.5%) died due to circulatory failure, and 1 patient dropped out. The remaining 34 (52.31%) patients (24 men and 10 women) formed the unsuccessful weaning group (Table 1). Compared with patients in the unsuccessful weaning group, patients in the successful weaning group had younger age ($p = 0.004$), lower APACHE II scores before ECMO ($p < 0.001$), lower percentage of renal insufficiency history ($p = 0.001$), lower lactate levels before ECMO ($p = 0.013$) and during ECMO ($p < 0.001$), higher MAP before ECMO ($p < 0.001$), higher PaO_2 during ECMO ($p < 0.001$) and a lower percentage of CRRT ($p < 0.001$).

The univariate analysis showed that age, lower APACHE II scores before ECMO, history of renal insufficiency, MAP before ECMO, PaO_2 during ECMO and the use of CRRT were significant factors for successful VV-ECMO weaning. After multivariate analysis was performed, lower APACHE II scores before ECMO (OR = 0.718; 95% CI = 0.542–0.951; p = 0.021) were identified as independent predictors for successful VV-ECMO weaning. The results of the univariate analysis and multivariate analyses are shown in Table 2 and Table 3 respectively. The results indicated that patients with severe ARDS of younger ages and lower APACHE II scores were more prone to wean from VV-ECMO successfully.

Table 1 Baseline Characteristics of the Patients in Two Groups

Variables	Successful Weaning Group (n=31)	Unsuccessful Weaning Group (n=34)	p value
Age, years, mean ± SD	45.8 ± 10.7	55.0± 13.6	0.004*
Males, n (%)	26 (83.90)	24 (70.60)	0.330
APACHE II scores before ECMO	17.60 ± 2.86	25.30 ± 4.55	< 0.001*
Cause of ARDS, n (%)			0.341
Pulmonary	28 (90.3)	33 (97.1)	
Extrapulmonary[a]	3 (9.7)	1 (2.9)	
Co-morbidities, n (%)			
Hypertension	4 (12.9)	7 (20.6)	0.621
Diabetes mellitus	3 (9.7)	4 (11.8)	0.999
Renal insufficiency	2 (6.45)	18 (52.9)	< 0.001*
Septic shock	4 (12.9)	4 (11.8)	0.999
Cardiac disease[b]	4 (12.9)	10 (29.4)	0.188
Ventilator-associated pneumonia	13 (41.9)	17 (50.0)	0.273

(*Continued*)

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Table 1 (Continued).

Variables	Successful Weaning Group (n=31)	Unsuccessful Weaning Group (n=34)	p value
BMI, kg/m^2, mean ± SD	23.33 ± 2.22	24.23 ± 2.37	0.209
Ventilation time, hours, median (IQR)	237 (116–351)	204 (86.5–308)	0.259
Tidal volume before ECMO, mL, mean ± SD	295 ± 26.7	296 ± 27.3	0.839
PEEP before ECMO, cmH_2O, mean ± SD	11.4 ± 1.66	10.7 ± 1.77	0.132
PaO_2/FiO_2 ratio, mmHg, mean ± SD	49.6 ± 6.51	48.4 ± 5.61	0.397
Arterial lactate levels before ECMO, mmol/L, median (IQR)	2.40 (2.00–3.50)	4.15 (2.90–5.30)	0.013*
Arterial lactate levels during ECMO, mmol/L, median (IQR)	2.20 (2.00–3.20)	4.50 (3.37–6.97)	< 0.001*
MAP before ECMO, mmHg, mean ± SD	72.1 ± 6.13	59.4 ± 9.58	< 0.001*
LVEF before ECMO, %, mean ± SD	51.8 ± 5.56	46.1 ± 5.04	< 0.001*
PaO_2 during ECMO, mmHg,	89.0 (80.0–98.0)	72.0 (68.2–77.5)	< 0.001*
ECMO duration, hours, median (IQR)	185.00 (94.0–255)	111 (71.5–234)	0.259
CRRT, n (%)	4 (12.9)	22 (64.7)	< 0.001*
Application of VA-ECMO	3 (9.7)	4 (11.8)	0.999

Notes: Renal insufficiency, [a]Trauma, pancreatitis, intraabdominal sepsis, subarachnoid hemorrhage. [b]Congestive heart failure, myocarditis, valvular disease. *p < 0.05.

Abbreviations: ECMO, extracorporeal membrane oxygenation; APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; BMI, body mass index; IQR, interquartile range; SD, standard deviation; PEEP, positive end-expiratory pressure; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; LVEF, left ventricular ejection fraction; CRRT, continuous renal replacement therapy.

Table 2 Univariate Analyses of the Predictors for Successful ECMO Weaning

Variables	OR	95% CI	p value
Age	0.939	0.896–0.983	0.008
APACHEII scores before ECMO	0.651	0.537–0.789	<0.001
Renal insufficiency	0.061	0.012–0.298	0.001
MAP before ECMO	1.246	1.114–1.392	<0.001
PaO2 during ECMO	1.083	1.033–1.135	0.001
Use of CRRT	0.08	0.022–0.285	<0.001

Abbreviations: ECMO, extracorporeal membrane oxygenation; APACHE II, Acute Physiology and Chronic Health Evaluation II; MAP, mean arterial pressure; PaO_2, partial pressure of arterial oxygen; CRRT, continuous renal replacement therapy; OR, odds ratio; CI, confidence interval.

Table 3 Multivariate Analyses of the Predictors for Successful ECMO Weaning

Variables	AOR	95% CI	p value
Age	0.969	0.898–1.046	0.426
APACHE II scores before ECMO	0.718	0.542–0.951	0.021*
Renal insufficiency	0.174	0.018–1.652	0.128
MAP before ECMO	1.099	0.920–1.312	0.296
PaO2 during ECMO	1.004	0.945–1.068	0.876
Use of CRRT	0.843	0.106–6.662	0.872

Note: *p < 0.05.

Abbreviations: ECMO, extracorporeal membrane oxygenation; APACHE II, Acute Physiology and Chronic Health Evaluation II; MAP, mean arterial pressure; PaO_2, partial pressure of arterial oxygen; CRRT, continuous renal replacement therapy; OR, odds ratio; CI, confidence interval.

Discussion

Many previous studies have evaluated the independent predictors for successful VA-ECMO weaning.[14–16] Veno-arterial ECMO is often used for cardiogenic shock, and the use of VV-ECMO in patients with respiratory failure has gradually increased.[17] Extracorporeal membrane oxygenation weaning is challenging during the use of VV-ECMO.[16] However, only a few studies are available for VV-ECMO weaning predictors. In this study, we retrospectively analysed predictors of successful weaning from VV-ECMO in patients with severe ARDS, which could provide a basis for clinicians to use VV-ECMO in the future. Our results indicated that patients with severe ARDS with lower APACHE II scores were more prone to wean from VV-ECMO successfully. Veno-venous ECMO is optimised for usability, acceptability and interpretability. This is a very general-purpose tool optimised for simplicity and widespread adoption, refining the predictive model based on clinical variables, which has not been taken into account by previous approaches. This is an important and core contribution of this study.

Veno-venous ECMO weaning decisions depend on ECMO pump flow and fresh gas flow.[18] For patients with severe ARDS, the weaning failure is high. Liu et al[4] retrospectively analysed data from 38 patients with severe ARDS. They found that 20 of 38 (52.63%) patients were weaned from VV-ECMO successfully.[4] Yeo et al[9] screened the data registered in Korea and found that 245 of 441 patients (55.6%) were successfully weaned from ECMO. Al-Fares et al[19] considered 83 patients weaned from VV-ECMO, of whom only 21 (25%) did not meet the criteria for safe liberation.

A lower APACHE II score is the other predictor we identified for successful VV-ECMO weaning, a finding that has important implications for clinical practice. The APACHE II classification system includes 12 physiological and laboratory parameters and 2 disease-related variables;[20,21] higher scores are associated with more severe disease.[22] In VV-ECMO treatment, the APACHE II score not only reflects the patients' physiological state but also provides clinicians with a basis for evaluating the patients' possibility of weaning. A lower APACHE II score usually means that the patient's physiological function is relatively good, and the degree of organ function damage is mild. This feature provides favourable conditions for patient recovery, thereby improving the success rate of VV-ECMO weaning. The value of the APACHE II scoring system to predict poor prognosis and mortality of severe disease has been determined by many previous studies.[20,23] Thus, this scoring system is often applied during patients' admission to an ICU. In recent years, using APACHE II scores to predict ECMO outcomes has been investigated. For instance, Yeh et al[24] reported that APACHE II was one of the risk factors associated with survival on VA-ECMO. Umei et al[25] indicated that the APACHE II score before ECMO was related to the oxygenator exchange during VV-ECMO. Furthermore, Liu et al[4] found that a higher APACHE II score was associated with unsuccessful weaning from ECMO. Consistent with previous studies, our study also indicated that lower APACHE II scores before ECMO were associated with successful weaning from ECMO. Understanding the relationship between APACHE II score and VV-ECMO weaning success can help clinicians make more accurate decisions during treatment. For patients with lower scores, earlier weaning evaluation may be considered to reduce the occurrence of ECMO-related complications. During VV-ECMO treatment, doctors can adjust treatment strategies based on scores and optimise patient supportive care. By identifying patients with high success rates, hospitals can allocate ECMO resources more effectively and improve overall treatment efficiency.

This study provides further evidence for predictors for successful weaning from VV-ECMO. Former studies also identified several other factors associated with ECMO weaning as well as APACHE II scores. For example, it has been reported that the ventilation time before ECMO was related to the risk of mortality. In Liu's study,[4] a longer duration of ventilation time before ECMO was reported to increase the rate of unsuccessful weaning from ECMO. However, we did not find a significant difference in ventilation time between the successful weaning group and the unsuccessful weaning group. Patients requiring renal replacement therapy during ECMO support has been regarded as a factor contributing to the mortality rate of ECMO weaning.[4] In the univariate analysis of our study, we found that the history of renal insufficiency and CRRT were significant factors for successful VV-ECMO weaning. However, these two factors were not included in the final logistic regression equation after the multivariate analysis. This may be due to the small sample size, the result of nuances in the data set or confounding by other predictors. The specific reasons for the differences in results require further research. Furthermore, subsequent designs should take a larger population and follow-up study into account.

When discussing the weaning off Veno-Venous Extracorporeal Membrane Oxygenation (VV-ECMO), gender differences are a factor that cannot be overlooked. Although the primary criteria for weaning off VV-ECMO do not vary by gender, the physiological and pathological differences between males and females may impact the weaning process. For instance, research indicates that females may exhibit recovery patterns in pulmonary function and oxygenation reserve that differ from those of males. Additionally, fluctuations in hormone levels, particularly estrogen levels in females, can affect inflammatory responses and vascular permeability, thereby influencing the success rate of weaning. Consequently, when weaning off VV-ECMO, physicians need to consider these gender-specific factors and develop personalized management strategies based on the patient's specific condition.

This study has some limitations. First, it is a single-centre study, which may cause selection bias. Second, the sample size of this study was relatively small. Finally, because of the retrospective nature, we did not include enough variables in our logistic regression analysis and may have overlooked some important ones.

Conclusions

For patients with severe ARDS supported by VV-ECMO, APACHE II scores before ECMO are independent predictors for successful VV-ECMO weaning.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding authors.

Ethics Approval and Consent to Participate

This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of the Gannan Medical College of Jiangxi Province in accordance with the Declaration of Helsinki. Owing to the retrospective nature of the study, The First Affiliated Hospital of Gannan Medical College of Jiangxi Province waived the need for informed consent. All patient records and data were anonymized and identified prior to the analysis.

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Disclosure

None of the authors had any personal, financial, commercial, or academic conflicts of interest.

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