Venovenous extra-corporeal membrane oxygenation for severe acute respiratory distress syndrome: a matched cohort study

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Abstract

Background: Although the use of extra-corporeal membrane oxygenation (ECMO) has been rapidly increasing, the benefit of ECMO in patients with acute respiratory distress syndrome (ARDS) remains unclear. Our objective was to investigate the effect of venovenous ECMO (VV-ECMO) on adult patients with severe ARDS.

Methods: We conducted a multi-center, retrospective, cohort study in the intensive care units (ICUs) of six teaching hospitals between January 2013 and December 2018. Patients with severe ARDS who received VV-ECMO support were included. The detailed demographic data and physiologic data were used to match ARDS patients without ECMO. The primary endpoint was the 28-day mortality.

Results: Ninety-nine patients with severe ARDS supported by VV-ECMO and 72 patients without ECMO were included in this study. The acute physiology and chronic health evaluation II score was 23.1 ± 6.3 in the ECMO group and 24.8 ± 8.5 in the control group (P = 0.1195). The sequential organ failure assessment score was 12.8 ± 3.4 in the ECMO group and 13.7 ± 3.5 in the control group (P = 0.0848). The 28-day mortality of patients with ECMO support was 39.4%, and that of the control group was 55.6%. The survival analysis curve showed that the 28-day mortality in the ECMO group was significantly lower than that in the control group (P = 0.0097). Multivariate Cox regression analysis showed that the independent predictors of the 28-day mortality were the requirement of vasopressors before ECMO (hazard ratio [HR]: 1.006; 95% confidence interval [CI]: 1.001–1.013; P = 0.030) and duration of mechanical ventilation before ECMO (HR: 3.299; 95% CI: 1.264–8.609; P = 0.034).

Conclusions: This study showed that ECMO improved the survival of patients with severe ARDS. The duration of mechanical ventilation and the requirement of vasopressors before ECMO might be associated with an increased risk of death.

Keywords: Acute respiratory distress syndrome; Extra-corporeal membrane oxygenation; Mortality; Multi-center; Mechanical ventilation.

Introduction

Acute respiratory distress syndrome (ARDS) is a severe clinical syndrome characterized by diffuse endothelial and epithelial injury, inflammatory pulmonary edema, and severe hypoxemia in the intensive care unit (ICU). Despite understanding the pathology, physiology, and mechanism of ARDS, as well as the progress of mechanical ventilation, the morbidity and mortality of ARDS remain unacceptably high.¹⁻³ Extra-corporeal membrane oxygenation (ECMO) is an alternative cardiopulmonary supportive device that confers a high-risk and high-cost.⁴⁻⁶ Although the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) study and observational studies showed that ECMO could improve survival of patients with severe ARDS,⁷⁻⁸ the recent ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial showed that ECMO does not decrease mortality compared with conventional therapy.⁹

Currently, although the utilization of ECMO in China increased dramatically, the benefit of ECMO in patients with ARDS remains unclear. We performed a matched cohort study retrospectively to evaluate the benefit and risk factors of ECMO in patients with severe ARDS. We...
hypothesized that ECMO could improve the survival of patients with severe ARDS.

Methods

Ethical approval
This retrospectively matched cohort study was approved by the Ethics Committee of Zhongda Hospital, School of Medicine, Southeast University, and the informed consent was waived due to the retrospective nature of the study.

Patients
This cohort study was performed in the ICU of six university teaching hospitals. Patients with ARDS requiring ECMO for respiratory support between January 2013 and December 2018 were included.

The inclusion criteria comprised the following: (1) age between 18 and 70 years; (2) severe ARDS with ECMO support; and (3) reversible causes of severe respiratory dysfunction.

The exclusion criteria comprised the following: (1) mechanical ventilation with high-level airway pressure (positive end-expiratory pressure [PEEP]) >15 cmH2O (1 cmH2O = 0.098 kPa) and/or plateau pressure (Pplat) >35 cmH2O for longer than 7 days; (2) persistent high concentration oxygen therapy (fraction of inspired oxygen [FiO2] >80%) for longer than 7 days; (3) severe active bleeding; (4) surgery within 24 hours or brain injury combined with intra-cranial bleeding; (5) severe irreversible status; (6) uncontrolled malignant tumor; (7) progressive pulmonary fibrosis; and (8) unresolved surgical issues.

ARDS patients with ECMO support were matched with ARDS patients without ECMO support in the same year. The method for case matching in the control group comprised selecting appropriate cases for matching according to the following criteria:

(1) The characteristics of the patients before ECMO support were recorded including the cause of ARDS, evaluation of disease severity (APACHE II score), and duration of ECMO support.

(2) The following parameters were reviewed and collected 1 day before ECMO support as well as on the second and third days after ECMO support:

(3) Pulmonary mechanics parameters, including the tidal volume (VT), Pplat, respiratory rate, and minute ventilation;

(4) Pulmonary gas exchange parameters, including the arterial blood pH value, PaO2, partial pressure of carbon dioxide, PaO2/FiO2, and lactic acid level;

(5) Hemodynamic parameters, including the required vasopressors before ECMO, mean arterial pressure (MAP), and norepinephrine dose or equivalence;

(6) Complications, such as bleeding, infection, and oxygenator failure;

(7) The primary outcome (28-day mortality) was recorded, as well as the outcome of up to 90 days.

(8) The secondary outcome measures, such as the duration of ECMO, ICU stay, and duration of mechanical ventilation before ECMO, were recorded.

Management of patients

In the ECMO group, cannulation was performed by percutaneous catheterization with a 21F to 23F venous catheter (Maquet, Hirrlingen, Germany) placed for the drainage of venous blood in the femoral vein, and a 17F to 19F catheter was placed in the right internal jugular vein to return oxygenated blood. A centrifugal pump (Maquet) and an oxygenator (Maquet) were operated using conventional settings. Conventional treatments were performed by the attending doctors in charge. The doctor performed daily evaluation and screening for patients to determine when the patients can be weaned from ECMO.

In the control group, a conventional lung-protective ventilation strategy was applied. The ventilation settings and hemodynamics were collected. Other treatments were performed routinely by the physician in charge.

The demographic data and prognostic data in both the ECMO and control groups were collected.

Data source and data collection

All the patient data related to the study were reviewed and collected. All the data were collected from the hospital information system and medical record. All the data were recorded using the data acquisition system provided by Medical System Company, Suzhou, Jiangsu, China.

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Statistical analysis

Continuous variables with normal distribution (Kolmogorov-Smirnov test) such as age, height, and pulmonary gas exchange parameters were expressed as the mean ± standard deviation, and categorical variables such as gender and requirement of vasopressors before ECMO were expressed as n (percentage). Student’s t test and Chi-squared test were used to detect differences between
two groups for continuous and categorical variables, respectively. Kaplan-Meier curves and log-rank tests were used to assess the time to death from the date of ECMO initiation to 28 days and 90 days. Cox proportional hazards models were used to evaluate the univariate and multivariate hazard ratios (HRs) for the risk predictors of mortality in the ECMO group. A candidate variable with a univariate \( P \leq 0.05 \) was retained in the multivariable model. A value of \( P < 0.05 \) was considered statistically significant. All statistical analyses were performed using SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 6.0 (GraphPad Software Inc., La Jolla, CA, USA).

## Results

### Characteristics of patients

Ninety-nine patients with ARDS received ECMO for respiratory support, and 72 matched control patients were included from six university hospitals (Zhongda Hospital of Southeast University, Peking Union Medical College Hospital, Nanjing Jiling Hospital, Medical School of Nanjing University, Suzhou Hospital Affiliated to Nanjing Medical University, Wuxi People’s Hospital Affiliated to Nanjing Medical University, and Hospital of Nantong University). There were 10, 13, 21, 16, 20, and 5 in control group from 2013 to 2018, respectively. Among the 99 patients supported with ECMO, 70 patients from Zhongda Hospital \( (n = 70) \), 13 patients from Peking Union Medical College Hospital \( (n = 13) \), six patients from Nanjing Jiling Hospital \( (n = 6) \), four patients from Suzhou Hospital \( (n = 4) \), three patients from Wuxi People’s Hospital \( (n = 3) \), three patients from Hospital of Nantong University \( (n = 3) \). The main demographic and clinical variables of the patients and disease severity before ECMO support were not significantly different between patients in the two groups [Table 1].

### Effects of ECMO on the outcome of patients with severe ARDS

Among the 99 patients in the ECMO treatment group, 39 patients died 28 days after ECMO support, and the mortality rate was 39.4%. Regarding the control group \( (n = 72) \), the 28-day mortality was 55.6% with 40 patients dead. The 90-day mortality in the ECMO group was 44.4%, while that in the control group was 62.5%. The survival analysis curve showed that the mortality in 28 days in the ECMO group was significantly lower than that in the matched control group \( (P = 0.0097) \) [Table 2 and Figure 1].

### Effects of venovenous ECMO on the respiratory mechanics and hemodynamics of patients with ARDS

The blood flow was 4.7 ± 0.6 L/min and gas flow was 4.0 ± 1.4 L/min during the first day on ECMO, the blood flow was 4.5 ± 0.6 L/min and gas flow was 3.8 ± 0.8 L/min during the second day after ECMO support. Respiratory mechanics were significantly improved after ECMO initiation. After 2 days of ECMO support, the blood gas analysis results revealed a dramatically improved \( \text{PaO}_2/\text{FiO}_2 \), and the difference was statistically significant \( (P = 0.001) \). Meanwhile, in the ECMO-supported group, the VT and airway Pplat were significantly decreased [Table 3].

### Table 1: Baseline characteristics in patients with ARDS.

| Characteristics                  | All \( (n = 171) \) | ECMO group \( (n = 99) \) | Control group \( (n = 72) \) | Statistics | \( P \) |
|----------------------------------|---------------------|---------------------------|-----------------------------|------------|------|
| Age (years)                      | 50.6 ± 14.9         | 48.6 ± 4.9                | 50.2 ± 5.3                  | 1.952^1    | 0.0525|
| Male                             | 124 (72.5)          | 72 (72.7)                 | 52 (72.2)                   | 0.073^1    | 0.9419|
| Height (cm)                      | 168.8 ± 7.0         | 169.4 ± 6.8               | 167.9 ± 7.2                 | 1.431^1    | 0.1542|
| Ideal body weight (kg)           | 64.5 ± 8.3          | 65.2 ± 8.1                | 63.6 ± 8.5                  | 1.207^1    | 0.2291|
| Actual body weight (kg)          | 70.3 ± 13.4         | 71.8 ± 14.1               | 68.1 ± 12.1                 | 1.879^1    | 0.0620|
| APACHE II                        | 23.8 ± 7.3          | 23.1 ± 6.3                | 24.8 ± 8.5                  | 1.565^1    | 0.1195|
| SOFA                             | 13.2 ± 3.4          | 12.8 ± 3.4                | 13.7 ± 3.5                  | 1.734^1    | 0.0848|
| Murray score                     | 3.5 ± 0.5           | 3.5 ± 0.5                 | 3.6 ± 0.5                   | 0.676^1    | 0.4999|
| MV duration before ECMO (h)      | –                   | 63.8 ± 53.0               | –                           | –          | –    |
| Requirement of vasopressors before ECMO | 116 (67.8) | 70 (70.7) | 46 (63.9) | 0.940^1 | 0.3474|
| pH                               | 7.34 ± 0.14         | 7.33 ± 0.15               | 7.34 ± 0.11                 | 0.113^1    | 0.9105|
| \( \text{PaO}_2/\text{FiO}_2 \) (mmHg) | 77.0 ± 29.6         | 75.0 ± 35.8               | 79.7 ± 17.5                 | 1.028^1    | 0.3053|
| \( \text{PaCO}_2 \) (mmHg)       | 45.4 ± 17.4         | 46.2 ± 19.6               | 44.3 ± 13.8                 | 0.697^1    | 0.4868|
| VT (mL/kg of predicted body weight) | 6.3 ± 1.5         | 6.2 ± 1.5                 | 6.5 ± 1.6                   | 1.414^1    | 0.1592|
| PEEP (cmH2O)                     | 14.4 ± 3.8          | 14.4 ± 3.7                | 14.4 ± 3.8                  | 0.001^2    | 0.9999|
| Pplat (cmH2O)                    | 29.0 ± 3.3          | 28.9 ± 3.7                | 29.2 ± 2.6                  | 0.001^3    | 0.9999|
| Driving Pressure (cmH2O)         | 14.6 ± 2.9          | 14.4 ± 2.9                | 15.0 ± 2.9                  | 0.001^4    | 0.9999|
| MAP (mmHg)                       | 89.8 ± 20.4         | 81.2 ± 13.1               | 101.9 ± 22.7                | 7.494^4    | 0.0001|
| NE (\( \mu \)g/min)             | 19.5 ± 26.8         | 22.1 ± 28.0               | 15.9 ± 24.8                 | 1.493^5    | 0.1374|
| Lactate (mmol/L)                 | 2.6 ± 2.1           | 2.4 ± 1.5                 | 2.9 ± 2.7                   | 1.684^1    | 0.0941|

Values are \( n \) (%) or mean ± standard deviation. *Chi-square value. \( 1 \text{mmHg} = 0.133 \text{kPa}, 1 \text{cmH}_2\text{O} = 0.098 \text{kPa}. – Not applicable. ECMO: Extra-corporeal membrane oxygenation; APACHE: Acute physiology and chronic health evaluation; SOFA: Sepsis-related organ failure assessment; MV: Mechanical ventilation; \( \text{PaO}_2 \): Partial pressure of \( \text{O}_2 \) in arterial blood; \( \text{FiO}_2 \): Fraction of inspired oxygen; \( \text{PaCO}_2 \): Partial pressure of \( \text{CO}_2 \) in arterial blood; VT: Tidal volume; PEEP: Positive end-expiratory pressure; Pplat: Plateau airway pressure; MAP: Mean artery pressure; NE: Norepinephrine.
Mechanical ventilation (days) 15.9
Mortality on 90 days 89 (52.0) 44 (44.4) 45 (62.5) 7.873
†
Hospital stay (days) 23.3
ICU stay (days) 21.0

ECMO related complications
The rate of ECMO related complications remained high. Bleeding complications occurred in 20 of the 99 patients in the ECMO treatment group, accounting for 20% of the total ECMO cases. Cannulation site bleeding was the most common complication in ECMO patients, affecting 11 patients. Intra-cranial bleeding occurred in one case and this patient died. Infection complications, including bloodstream infections, ventilator-associated pneumonia, and cannula site infections occurred in 6%, 4%, and 8% of the ECMO patients, respectively [Table 4].

Predictor for 28 days mortality of ECMO patients
Ninety-nine patients with severe ARDS who received ECMO were included in this study. The MAP was lower in the non-survivor group than in the survivor group. The requirement of vasopressors before ECMO in the survivor group was less than in the non-survivor group. The duration of mechanical ventilation before ECMO and duration of ECMO were both longer in the non-survivor group than in the survivor group [Table 5].

Univariate Cox regression analysis was performed to determine the risk factors associated with the outcome of ECMO patients. The duration of mechanical ventilation before ECMO, requirement of vasopressors before ECMO, and MAP before ECMO were demonstrated as important factors for the poor prognosis of patients [Table 6].

Multivariate logistic regression analysis showed that the duration of mechanical ventilation before ECMO and requirement of vasopressors before ECMO were independent risk factors associated with a poor prognosis [Table 7].

Discussion
In this retrospective matched cohort study, we found that patients with severe ARDS supported with venovenous ECMO (VV-ECMO) were associated with a reduction in the 28-day and 90-day mortality compared with matched patients without ECMO support. The duration of mechanical ventilation and requirement of vasopressors before ECMO initiation were independent risk factors accompanied with high mortality.

ECMO is an alternative support for severe ARDS. The two negatively randomized clinical trials failed to demonstrate the benefit of ECMO in adult respiratory failure patients,[8,9] while the CESAR study showed that the transfer of reversible severe acute respiratory failure patients to the ECMO center significantly improved the 6-month outcome.[5] Subsequently, ECMO played an important role in the treatment of severe ARDS caused by viral pneumonia.[10,11] In China, ECMO has developed rapidly,[12] and many ECMO centers have been established in the last 5 years. However, the effect of ECMO on patients with ARDS has not been well clarified.[13]

This retrospective study evaluated the efficacy and safety of ECMO in China. Because the patients supported with high-pressure and high-volume ventilation have a poor outcome even with ECMO support, we excluded those with high-level mechanical ventilation for more than 7 days. Our results showed that ECMO could significantly improve the survival rate compared with the matched control group, confirming the benefit of ECMO for patients with severe ARDS.[14] The survival rate of patients with ARDS supported with ECMO at 90 days was still high,[13] up to 44.4% in this study. Two-thirds of the patients required vasopressors before the initiation of ECMO; however, the efficacy of application of ECMO in septic shock patients remains controversial.[15]
Infections 18 (18)
Bloodstream infections 6 (6)
VAP 4 (4)
Cannula site infections 8 (8)

Values are n (%). *Cannula-related problems mean need to change the Cannula. ECMO: Extra-corporeal membrane oxygenation; VAP: Ventilator-associated pneumonia.

Table 3: Effects of VV-ECMO on the respiratory mechanics and hemodynamics of patients with ARDS.

| Characteristics | All (n = 171) | ECMO group (n = 99) | Control group (n = 72) | t    | P    |
|----------------|--------------|-------------------|-----------------------|------|------|
| 2 days after ECMO support |              |                   |                       |      |      |
| VT (mL/kg of IBW) | 4.9 ± 1.7    | 3.7 ± 0.9         | 6.5 ± 1.1             | 18.035 | <0.0001 |
| PEEP (cmH2O)     | 11.9 ± 2.4   | 11.4 ± 2.3        | 12.7 ± 2.4            | 3.881 | 0.0001 |
| Pplat (cmH2O)    | 23.7 ± 4.7   | 21.2 ± 4.5        | 27.1 ± 2.4            | 5.832 | <0.0001 |
| PaO2/FiO2 (mmHg) | 38.7 ± 9.5   | 36.3 ± 7.6        | 42.0 ± 10.7           | 4.105 | 0.0001 |
| Lactate (mmol/L) | 2.5 ± 2.2    | 2.9 ± 2.6         | 2.3 ± 1.8             | 0.851 | 0.0659 |
| NE (µg/min)      | 22.8 ± 24.7  | 24.4 ± 25.0       | 20.5 ± 24.3           | 1.010 | 0.3121 |
| MAP (mmHg)       | 79.5 ± 11.8  | 79.1 ± 13.7       | 79.8 ± 10.3           | 0.340 | 0.7379 |
| 3 days after ECMO support |              |                   |                       |      |      |
| VT (mL/kg of IBW) | 4.9 ± 1.7    | 3.8 ± 1.1         | 6.4 ± 1.3             | 13.359 | <0.0001 |
| PEEP (cmH2O)     | 11.6 ± 2.5   | 10.9 ± 2.4        | 12.5 ± 2.4            | 4.055 | <0.0001 |
| Pplat (cmH2O)    | 23.6 ± 4.8   | 20.9 ± 3.8        | 27.2 ± 3.6            | 11.060 | <0.0001 |
| pH              | 7.39 ± 0.08  | 7.42 ± 0.07       | 7.37 ± 0.10           | 3.923 | 0.0001 |
| PaO2/FiO2 (mmHg) | 152.4 ± 69.9 | 180.5 ± 74.8      | 113.8 ± 36.9          | 6.976 | <0.0001 |
| PaCO2 (mmHg)    | 41.2 ± 9.3   | 39.2 ± 7.3        | 44.1 ± 11.0           | 3.470 | 0.0007 |
| Lactate (mmol/L) | 2.1 ± 1.3    | 2.1 ± 1.4         | 2.1 ± 1.1             | 0.133 | 0.8947 |
| NE (µg/min)      | 18.7 ± 19.7  | 18.9 ± 22.8       | 18.5 ± 14.6           | 0.104 | 0.9177 |
| MAP (mmHg)       | 85.5 ± 12.8  | 85.7 ± 10.5       | 85.2 ± 15.4           | 0.282 | 0.7782 |
| SOFA             | 10.8 ± 4.3   | 9.1 ± 3.5         | 13.0 ± 4.4            | 6.503 | <0.0001 |

1 cmH2O = 0.098 kPa, 1 mmHg = 1.33 kPa. VV-ECMO: Venovenous extra-corporeal membrane oxygenation; ARDS: Acute respiratory distress syndrome; VT: Tidal volume; IBW: Ideal body weight; PEEP: Positive end-expiratory pressure; Pplat: Plateau airway pressure; PaO2: Partial pressure of O2 in arterial blood; FiO2: Fraction of inspired oxygen; PaCO2: Partial pressure of CO2 in arterial blood; NE: Norepinephrine; MAP: Mean artery pressure; SOFA: Sepsis-related organ failure assessment.

After ECMO initiation, protective mechanical ventilation was used to prevent further ventilator-induced lung injury. A high VT and high transpulmonary pressure caused lung injury,[16] and an even worse outcome.[17] Studies have shown that tidal hyperinflation exacerbates the local inflammatory reaction despite the small VT and pressure limitation in patients with a larger non-aerated compartment.[18] With ECMO support or CO2 removal, a further decrease in the VT of patients with severe ARDS could reduce lung injury and achieve ultra-protective lung ventilation.[19] In this study, when patients with ARDS were supported by ECMO, the ventilator setting was significantly decreased, and the VT and transpulmonary pressure were reduced, improving the outcome of the patients.

The management of ECMO support requires teamwork and multidisciplinary cooperation. Coagulation and anti-coagulation disorders can cause bleeding and clot formation, leading to oxygenator failure and the need for the changing circuit of ECMO. It was shown that bleeding is the most common complication of ECMO.[13] Our study showed that the incidence of bleeding complications was up to 20% in patients on VV-ECMO. Most bleeding complications occurred at the cannulation site. Intracranial hemorrhage was the most frequent type of neurologic complication, and the survival of patients with neurologic injury was poor.[20,21] Furthermore, mechanical complications such as tube kinking and centrifugal pump dysfunction were also important factors that impacted the ECMO circuit and oxygenator survival time.

This study possessed some limitations. First, this was a non-randomized, retrospective, observational study, and may have been subject to bias. Second, this was a multicenter study performed at teaching hospitals. However, most of the patients with ARDS included were from one hospital; only a few patients were included from other hospitals in the first 3 years. A higher average annual ECMO case volume was associated with an improved outcome.[22] A lack of ECMO experience was associated with a higher incidence of complications. Third, the sample size of this study was not sufficiently large. Finally, only 15 patients were matched in the control group but 39 patients in the ECMO group in the last 2 years because the young patients were prone to be supported by ECMO if they fulfill the criteria, especially in recent years.
### Table 5: Effects of VV-ECMO on characteristics of patients with ARDS.

| Characteristics                          | Survivor group (n = 60) | Non-survivor group (n = 39) | Statistics | P     |
|------------------------------------------|-------------------------|-----------------------------|------------|-------|
| Age (years)                              | 46.5 ± 13.9             | 44.5 ± 14.8                 | 0.690†     | 0.492 |
| Male                                     | 41 (68.3)               | 31 (79.5)                   | 3.544‡     | 0.460 |
| Ideal body weight (kg)                   | 65.8 ± 8.2              | 64.3 ± 8.1                  | 0.894‡     | 0.373 |
| APACHE II before ECMO                    | 22.2 ± 6.0              | 24.1 ± 6.4                  | 1.522†     | 0.131 |
| SOFA before ECMO                         | 12.2 ± 3.2              | 13.5 ± 3.4                  | 1.888†     | 0.062 |
| Murray score before ECMO                 | 3.5 ± 0.5               | 3.6 ± 0.5                   | 1.050†     | 0.296 |
| MV duration before ECMO (h)              | 53.8 ± 41.8             | 76.3 ± 62.3                 | 2.135‡     | 0.035 |
| Tidal volume (mL/kg IBW)                 | 6.2 ± 1.5               | 6.2 ± 1.7                   | 0.133†     | 0.895 |
| PEEP (cmH₂O)                             | 14.4 ± 3.6              | 14.5 ± 3.9                  | 0.024†     | 0.981 |
| Pplat (cmH₂O)                            | 28.1 ± 5.5              | 25.6 ± 8.0                  | 3.115†     | 0.084 |
| Driving pressure (cmH₂O)                 | 17.6 ± 4.8              | 18.4 ± 5.8                  | 0.778†     | 0.382 |
| pH before ECMO                           | 7.32 ± 0.20             | 7.35 ± 0.10                 | 0.754‡     | 0.452 |
| PaO₂/FiO₂ (mmHg)                         | 77.8 ± 42.1             | 71.6 ± 26.0                 | 0.859‡     | 0.393 |
| PaCO₂ (mmHg)                             | 47.4 ± 22.2             | 44.7 ± 15.7                 | 0.684‡     | 0.496 |
| Requirement of vasopressors before ECMO  | 36 (60.0)               | 34 (87.2)                   | 2.889‡     | 0.039 |
| NE dose before ECMO (μg/min)             | 19.3 ± 28.8             | 25.3 ± 27.2                 | 1.065†     | 0.290 |
| MAP (mmHg)                               | 83.4 ± 13.5             | 77.9 ± 11.8                 | 2.131†     | 0.036 |
| Lactate (mmol/L)                         | 2.3 ± 1.5               | 2.5 ± 1.6                   | 0.521‡     | 0.604 |
| ECMO duration (days)                     | 10.7 ± 5.1              | 13.4 ± 7.7                  | 2.103†     | 0.038 |
| ICU stay (days)                          | 28.6 ± 18.2             | 21.7 ± 17.3                 | 1.929†     | 0.057 |

Values are n (%) or mean ± standard deviation. †T value, ‡Chi-square value. Driving pressure = plateau airway pressure – positive end-expiratory pressure. 1 cmH₂O = 0.098 kPa, 1 mmHg = 0.133 kPa. VV-ECMO: Venovenous extra-corporeal membrane oxygenation; ARDS: Acute respiratory distress syndrome; APACHE: Acute physiology and chronic health evaluation; SOFA: Sepsis-related organ failure assessment; MV: Mechanical ventilation; IBW: Ideal body weight; PEEP: Positive end-expiratory pressure; Pplat: Plateau airway pressure; PaO₂: Partial pressure of O₂ in arterial blood; FiO₂: Fraction of inspired oxygen; PaCO₂: Partial pressure of CO₂ in arterial blood; NE: Norepinephrine; MAP: Mean artery pressure; ICU: Intensive care unit.

### Table 6: Cox regression analysis for 28-day mortality of patients with ECMO.

| Characteristics                          | Hazard ratio | 95% Confidence limits | P     |
|------------------------------------------|--------------|-----------------------|-------|
| Age                                      | 1.004        | 0.983                 | 1.024 | 0.726 |
| Gender                                   | 0.423        | 0.126                 | 1.425 | 0.165 |
| BMI                                      | 0.981        | 0.831                 | 1.171 | 0.819 |
| APACHE II                                | 1.041        | 0.987                 | 1.097 | 0.137 |
| SOFA                                     | 1.104        | 0.995                 | 1.225 | 0.061 |
| MV duration before ECMO                  | 1.006        | 1.000                 | 1.011 | 0.038 |
| pH before ECMO                           | 1.949        | 2.56                 | 14.872 | 0.520 |
| PaO₂/FiO₂ before ECMO                    | 0.997        | 0.987                 | 1.006 | 0.484 |
| PaCO₂ before ECMO                        | 0.995        | 0.978                 | 1.012 | 0.581 |
| Requirement of vasopressors before ECMO  | 3.179        | 1.342                 | 7.530 | 0.009 |
| NE                                       | 1.143        | 0.994                 | 1.012 | 0.469 |
| MAP before ECMO                          | 0.972        | 0.947                 | 0.997 | 0.030 |
| Lactate                                  | 1.047        | 0.866                 | 1.265 | 0.634 |
| Pplat                                    | 1.019        | 0.955                 | 1.088 | 0.550 |
| Driving pressure"                        | 1.116        | 1.001                 | 1.245 | 0.048 |
| Creatine                                 | 0.960        | 0.839                 | 1.098 | 0.552 |
| Blood urea nitrogen                      | 0.976        | 0.921                 | 1.034 | 0.415 |
| NE after ECMO                            | 1.004        | 0.994                 | 1.015 | 0.380 |
| PaO₂/FiO₂ after ECMO                     | 0.998        | 0.991                 | 1.005 | 0.605 |
| PaCO₂ after ECMO                         | 1.029        | 0.992                 | 1.068 | 0.124 |

"Driving pressure = plateau pressure – positive end-expiratory pressure. ECMO: Extra-corporeal membrane oxygenation; BMI: Body mass index; APACHE: Acute physiology and chronic health evaluation; SOFA: Sepsis-related organ failure assessment; MV: Mechanical ventilation; PaO₂: Partial pressure of O₂ in arterial blood; FiO₂: Fraction of inspired oxygen; PaCO₂: Partial pressure of CO₂ in arterial blood; NE: Norepinephrine; MAP: Mean artery pressure; ICU: Intensive care unit.
Finally, in this cohort of patients with severe ARDS, VV-ECMO improves the survival rate as an effective respiratory support for patients with severe ARDS. In patients with ARDS who received ECMO, the duration of mechanical ventilation and the requirement of vasopressors before ECMO were associated with a higher 28-day mortality.

**Funding**

This work was supported by grants from the Jiangsu Province’s Key Discipline/Laboratory of Medicine (No. ZDXKA2016025), the Jiangsu Province’s Key Provincial Talents Program (No. ZDRCA2016082), and the National Natural Science Foundation of China (No. 81370180).

**Conflicts of interest**

None.

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