

Extended Use of Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome: A Retrospective Multicenter Study

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Background: Beyond its current function as a rescue therapy in acute respiratory distress syndrome (ARDS), extracorporeal membrane oxygenation (ECMO) may be applied in ARDS patients with less severe hypoxemia to facilitate lung protective ventilation. The purpose of this study was to evaluate the efficacy of extended ECMO use in ARDS patients.

Methods: This study reviewed 223 adult patients who had been admitted to the intensive care units of 11 hospitals in Korea and subsequently treated using ECMO. Among them, the 62 who required ECMO for ARDS were analyzed. The patients were divided into two groups according to pre-ECMO arterial blood gas: an extended group (n=14) and a conventional group (n=48).

Results: Baseline characteristics were not different between the groups. The median arterial carbon dioxide tension/fraction of inspired oxygen (FiO₂) ratio was higher (97 vs. 61, p<0.001) while the median FiO₂ was lower (0.8 vs. 1.0, p<0.001) in the extended compared to the conventional group. The 60-day mortality was 21% in the extended group and 54% in the conventional group (p=0.03). Multivariate analysis indicated that the extended use of ECMO was independently associated with reduced 60-day mortality (odds ratio, 0.10; 95% confidence interval, 0.02–0.64; p=0.02). Lower median peak inspiratory pressure and median dynamic driving pressure were observed in the extended group 24 hours after ECMO support.

Conclusion: Extended indications of ECMO implementation coupled with protective ventilator settings may improve the clinical outcome of patients with ARDS.

Keywords: Extracorporeal Membrane Oxygenation; Respiratory Distress Syndrome, Adult; Respiration, Artificial; Retrospective Studies; Multicenter Studies as Topic

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Introduction

Acute respiratory distress syndrome (ARDS) is characterized by lung injury caused by either direct or indirect insults and leads to severe respiratory failure that is refractory to conventional oxygen therapy^{1,2}. Hospital mortality in patients with severe ARDS ranges from 45% to 60%²⁻⁴. Mechanical ventilation is the mainstay of ARDS therapy. However, overdistention and cyclic alveolar recruitment and de-recruitment during ventilation may further damage lungs and increase inflammatory mediators, eventually resulting in multiple organ failure and death⁵. Lung protective ventilation strategies using low tidal volume and higher levels of positive end-expiratory pressure (PEEP) are widely accepted approaches^{6,7}, although rescue therapies may still be required in refractory cases.

Extracorporeal membrane oxygenation (ECMO) can provide adequate blood carbon dioxide removal and oxygenation, allowing a reduction in mechanical ventilation and minimization of ventilator-induced lung injury (VILI). Several clinical trials in ARDS have shown positive results of venovenous-ECMO^{3,8,9}. Although there are no absolute criteria for ECMO initiation in ARDS, suggested indications include severe hypoxemia (arterial carbon dioxide tension [PaO₂]/fraction of inspired oxygen [FiO₂] ratio <80 on FiO₂ >0.9), uncompensated hypercapnia with acidemia, or excessively elevated end-inspiratory plateau pressures despite standard ventilator management¹⁰. Venovenous-ECMO may be applied in ARDS patients with less severe hypoxemia in whom it might allow "lung rest" by lowering airway pressures and tidal volume rather than improving oxygenation, considering that there is a linear relationship between mortality and plateau pressure, even at less than 30 cm H₂O¹¹. Moreover, lung hyperinflation occurs in approximately 30% of ARDS patients ventilated using the protective ARDS Network strategy¹².

To date, there are limited data on the impact of initiation of ECMO in patients with less severe forms of ARDS. Accordingly, the aim of this study was to compare the clinical characteristics of patients who underwent ECMO for ARDS with less severe hypoxemia (namely "extended indications") versus conventional indications.

Materials and Methods

1. Study design and patient selection

This study was a retrospective analysis of a prospective multicenter cohort. The cohort was composed of critically ill adult patients who were at least 18 years old, received ECMO therapy, and were admitted to one of the intensive care units (ICUs) of the 11 participating tertiary or referral hospitals of Korea from January 2014 to December 2015. From this cohort, we included in our analysis patients who required ECMO sup-

port for ARDS. The exclusion criteria were as follows: received lung transplantation (either bridge to transplant or destination therapy), cardiopulmonary resuscitation before ECMO, ECMO transferred from other hospital, venoarterial-ECMO, acute respiratory diagnosis other than ARDS, and incomplete data for analysis. According to the pre-ECMO arterial blood gas, patients were divided into extended (PaO₂/FiO₂ ratio ≥80 without uncompensated respiratory acidosis) and conventional (PaO₂/FiO₂ ratio <80 on FiO₂ >0.9 and/or arterial carbon dioxide tension [PaCO₂] ≥80 mm Hg with pH <7.15) groups. The PaO₂/FiO₂ cutoff of 80 was selected based on recently proposed criteria for initiating ECMO in ARDS patients¹⁰. The primary study outcome was 60-day mortality. Secondary outcomes included ECMO duration, ECMO weaning failure rate, mechanical ventilation weaning success rate, mechanical ventilation-free days at day 60, and 30- and 90-day mortality. We also analyzed factors associated with 60-day mortality, including extended ECMO use. The local institutional review board or independent ethics committee of each hospital approved the study protocol (Institutional Review Board of Asan Medical Center, No. 2016-0269). Written informed consent was waived due to the observational nature of the study, and the patient records were anonymized and de-identified prior to analysis.

2. Data collection and definitions

Baseline demographic and clinical characteristics were collected and included age, sex, body mass index, immune status, etiologies of ARDS, dates of hospital and ICU admission, date of initiation of mechanical ventilation and ECMO, and treatment prior to ECMO. Acute Physiology and Chronic Health Evaluation (APACHE) II¹³ and Sequential Organ Failure Assessment (SOFA)¹⁴ scores were also collected at the time of ICU admission and ECMO initiation, respectively. The severity of ARDS before ECMO initiation was assessed by the PRedicting dEath for SEvere ARDS on VV-ECMO (PRESERVE) score¹⁵ and the Respiratory ECMO Survival Prediction (RESP) score¹⁶ as previously described. The pre-ECMO variables included rescue therapies (neuromuscular blocker, inhaled nitric oxide, or prone positioning), ventilator settings, and arterial blood gas. Ventilator settings included PEEP, peak inspiratory pressure, dynamic driving pressure (the difference between peak inspiratory pressure and PEEP)¹⁷, tidal volume, respiratory rate, and FiO₂, which were determined at baseline (before ECMO application) and at 4 hours and 24 hours thereafter. ARDS was diagnosed by consensus definition². An immunocompromised status was diagnosed if there was an underlying disease that affected the immune system (chronic liver disease, chronic kidney disease, human immunodeficiency virus infection, or malignancy) or if immunosuppressive therapy was being administered at the time of ECMO initiation. Steroid use was defined as corticosteroid adminis-

tration within 14 days of ECMO initiation.

3. Statistical analysis

Continuous variables are presented as median and interquartile range or as mean±standard deviation, whereas categorical variables are presented as percentages. Continuous variables were compared using a Mann–Whitney U test or Student’s t test. Categorical variables were compared using a chi-square or Fisher exact test. Binary logistic regression was used to identify factors predicting 60-day mortality. Variables with p-values <0.20 in the univariate analysis were included in the multivariate analysis by using stepwise backward selection procedures. Highly correlated variables were identified to prevent multicollinearity. Model discrimination was assessed with the area under the receiver operating characteristic curve, and model calibration was assessed with the Hosmer–Lemeshow test. A Cox proportional hazards regression model with stepwise backward selection procedures was also applied. The Kaplan–Meier curve was rendered to compare 60-day survival among the groups. All tests of significance were two-tailed, and p-values of <0.05 were considered significant. All analyses were performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

There were 223 patients in the initial cohort; 161 were not included for the following reasons: met specific exclusion criteria (n=90); ECMO provided for an acute respiratory diag-

nosis other than ARDS (n=68); and pre-ECMO arterial blood gas unavailable for analysis (n=3). Our study consisted of 62 ARDS patients who received ECMO as a rescue therapy. There were 14 patients (23%) in the extended group and 48 (77%) in the conventional group (Figure 1).

The baseline characteristics of the study patients are shown in Table 1. The percentage of male patients was significantly higher in the extended than in the conventional group, but there were no differences in age or body mass index. The proportion of immunocompromised patients was also similar between the two groups. In both groups, the main etiology of ARDS was bacterial pneumonia, followed by viral pneumonia. There were no differences between the groups in baseline APACHE II and SOFA scores, treatment prior to ECMO, and pre-ECMO rescue therapies. There was no difference between the groups in time from intubation to ECMO cannulation. The median PRESERVE and RESP scores were similar between the two groups (4 [3–6] vs. 5 [4–6], p=0.50; and 3 [0–5] vs. 2 [1–4], p=0.33, respectively). Compared with the conventional group, the extended group had a significantly higher median PaO₂/FiO₂ ratio (97 [88–112] vs. 61 [53–70], p<0.001) and lower median FiO₂ (0.8 [0.7–1.0] vs. 1.0 [1.0–1.0], p<0.001). Other ventilator settings before ECMO support were not significantly different between the two groups.

Clinical outcomes of the study patients are shown in Table 2. The primary outcome, 60-day mortality, was observed in three of the 14 patients (21%) in the extended group and 26 of the 48 patients (54%) in the conventional group (p=0.03). In addition, 90-day mortality was significantly lower in the extended group (3/14, 21%) than in the conventional group (27/48, 56%) (p=0.02), although the 30-day mortality rate

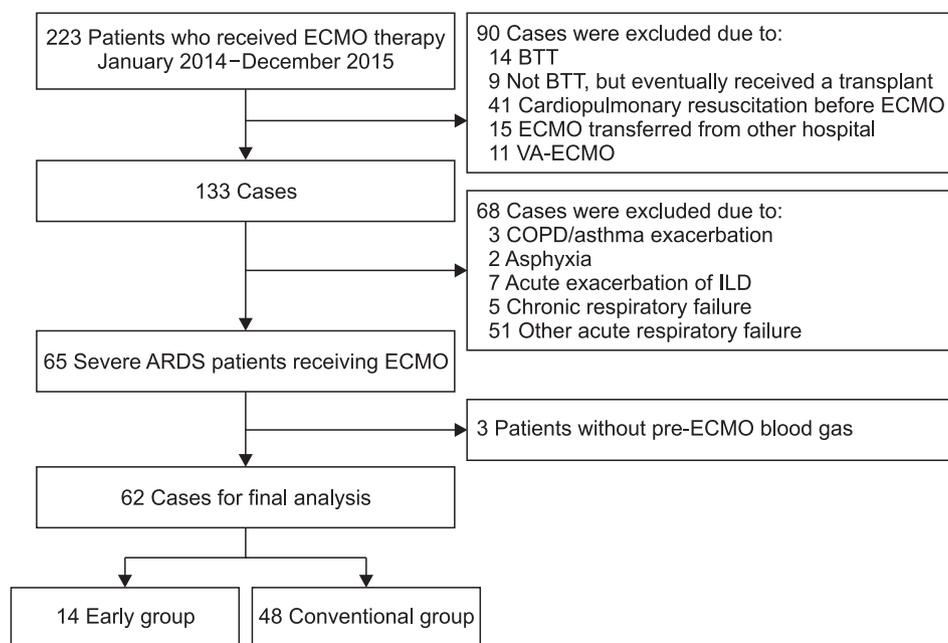


Figure 1. Illustration of a study flow diagram. ECMO: extracorporeal membrane oxygenation; BTT: bridge to transplant; VA: venoarterial; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; ARDS: acute respiratory distress syndrome.

Table 1. Baseline characteristics of the study patients

Variable	Extended group (n=14)	Conventional group (n=48)	p-value
Age, yr	50 (35–61)	59 (46–65)	0.21
Male sex	14 (100)	31 (65)	0.007
Body mass index, kg/m ²	24.9 (21.3–26.9)	23.3 (20.6–25.0)	0.19
Immunocompromised	2 (14)	9 (19)	>0.99
ARDS etiology			0.57
Viral pneumonia	4 (29)	13 (27)	
Bacterial pneumonia	8 (57)	32 (67)	
Trauma/burn	2 (14)	3 (6)	
APACHE II score at ICU admission	20 (12–25)	19 (14–26)	0.96
SOFA score at ECMO initiation	13 (11–16)	11 (7–14)	0.07
Pre-ECMO renal replacement therapy	3 (21)	10 (21)	>0.99
Pre-ECMO steroids	2 (14)	6 (13)	>0.99
Pre-ECMO bicarbonate infusion	2 (14)	8 (17)	>0.99
Pre-ECMO rescue therapy			
Neuromuscular blocker	10 (71)	35 (73)	>0.99
Inhaled nitric oxide	6 (43)	12 (25)	0.32
Prone positioning	6 (43)	22 (46)	0.84
Time between MV-ECMO, day	1.5 (1.0–5.0)	1.0 (0–3.5)	0.43
PRESERVE score	4 (3–6)	5 (4–6)	0.50
RESP score	3 (0–5)	2 (1–4)	0.33
Pre-ECMO ventilator settings			
Positive end-expiratory pressure, cm H ₂ O	10 (10–12)	10 (8–12)	0.60
Peak inspiratory pressure, cm H ₂ O	28 (27–30)	28 (23–30)	0.67
Dynamic driving pressure, cm H ₂ O	17 (15–20)	16 (14–20)	0.58
Tidal volume, mL	436 (350–512)	390 (300–600)	0.83
Respiratory rate, breaths/min	23 (20–28)	22 (16–27)	0.37
FiO ₂	0.8 (0.7–1.0)	1.0 (1.0–1.0)	<0.001
Pre-ECMO arterial blood gas			
pH	7.29 (7.23–7.40)	7.26 (7.17–7.33)	0.15
PaCO ₂ , mm Hg	47 (40–50)	52 (38–66)	0.17
PaO ₂ , mm Hg	84 (67–94)	60 (53–69)	<0.001
PaO ₂ /FiO ₂	97 (88–112)	61 (53–70)	<0.001
Bicarbonate, mEq/L	22.1 (18.7–25.0)	22.0 (18.1–26.7)	0.87

Values are presented as median (interquartile range) or number (%).

ARDS: acute respiratory distress syndrome; APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment; ECMO: extracorporeal membrane oxygenation; MV: mechanical ventilation; PRESERVE: PRedicting dEath for SEvere ARDS on VV-ECMO; RESP: Respiratory ECMO Survival Prediction; FiO₂: fraction of inspired oxygen; PaCO₂: arterial carbon dioxide tension; PaO₂: arterial oxygen tension.

was comparable between the groups. The median duration of ECMO was 8.0 (4.0–14.0) days in the extended group and 9.0 (6.0–23.5) days in the conventional group (p=0.37). There were no differences between the groups in the ECMO wean-

ing failure rate and tracheostomy rate. Both the mechanical ventilation weaning success rate and mechanical ventilation-free days at day 60 tended to be more favorable in the extended than in the conventional group, although the results were

not statistically significant. The Kaplan–Meier survival curves of the study patients are shown in Figure 2.

The results of univariate and multivariate analyses of risk factors predicting 60-day mortality are shown in Table 3. Multivariate analysis indicated that inhaled nitric oxide as pre-ECMO rescue therapy was significantly associated with mortality. Conversely, extended ECMO use was a protective factor (odds ratio, 0.10; 95% confidence interval, 0.02–0.64; $p=0.02$). This model had acceptable discrimination (area under the receiver operating characteristic curve=0.72) and calibration (Hosmer and Lemeshow chi-square=1.10; $p=0.58$). Consistently, inhaled nitric oxide and extended ECMO use were independently associated with “time to 60-day mortality” using Cox proportional hazards modeling (Table 4).

The changes in ventilator settings between the study groups during the 24-hour study period are shown in Figure 3 and Supplementary Table S1. After ECMO support, tidal volume, respiratory rate, and FiO_2 were decreased, but there were no significant differences between the extended and conventional groups until 24 hours. Both peak inspiratory pressure and dynamic driving pressure were decreased after ECMO initiation. The extended group had significantly lower median peak inspiratory pressure after 24-hour ECMO support (20 [18–20] $\text{cm H}_2\text{O}$ vs. 22 [20–24] $\text{cm H}_2\text{O}$, $p=0.006$). The extended group also tended to have lower median dynamic driving pressure after 24-hour ECMO support (10 [10–12] $\text{cm H}_2\text{O}$ vs. 12 [10–15] $\text{cm H}_2\text{O}$, $p=0.13$).

Discussion

The present study revealed a lower mortality rate in patients who received ECMO for ARDS with an extended indication, and extended ECMO use itself was positively associated with survival. The 54% 60-day mortality in the conventional group (where the median PRESERVE and RESP scores at ECMO

initiation were 5 and 2, respectively) is comparable with the 43%–46% mortality rates reported in previous studies of similar ECMO-treated ARDS patients^{15,16}. However, despite comparable severity at ECMO initiation, mortality was lower than expected in the extended group. In the extended group, lower median peak inspiratory pressure and median dynamic driving pressure were observed within 24 hours after ECMO initiation. These findings suggest that extended indications of ECMO implementation than conventional indications accompanied by an additional “lung rest” may improve the clinical outcome. To our knowledge, this is one of the few studies to evaluate the role of extended ECMO use in patients with ARDS.

Lung protective ventilator settings that keep tidal volume and plateau pressures within narrow limits should be used in ARDS patients to improve outcomes and prevent the development of VILI¹⁸. However, when there is dramatic hypoxemia and/or profound acidosis with a high degree of hypercapnia,

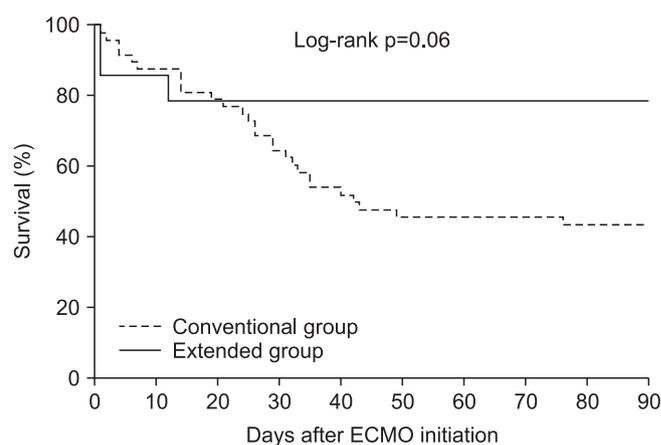


Figure 2. Kaplan–Meier survival curves of the patients under study. ECMO: extracorporeal membrane oxygenation.

Table 2. Clinical outcomes of the study patients

Variable	Extended group (n=14)	Conventional group (n=48)	p-value
ECMO duration, day	8.0 (4.0–14.0)	9.0 (6.0–23.5)	0.37
ECMO weaning failure	4 (29)	18 (38)	0.75
Tracheostomy	6 (43)	26 (55)	0.41
MV weaning success	8 (57)	17 (35)	0.15
MV-free days at day 60	23.3±24.7	16.1±23.4	0.35
Mortality			
30-Day	3 (21)	17 (35)	0.52
60-Day	3 (21)	26 (54)	0.03
90-Day	3 (21)	27 (56)	0.02

Values are presented as median (interquartile range), number (%), or mean±standard deviation. ECMO: extracorporeal membrane oxygenation; MV: mechanical ventilation.

Table 3. Univariate and multivariate analysis of factors associated with 60-day mortality

Variable	Unadjusted OR (95% CI)	p-value	Adjusted OR* (95% CI)	p-value
Age	1.03 (0.99–1.07)	0.16	-	-
Male sex	0.51 (0.17–1.59)	0.25	-	-
Bacterial pneumonia	1.93 (0.67–5.63)	0.23	-	-
Trauma/burn	0.26 (0.03–2.46)	0.24	-	-
APACHE II score at ICU admission	1.04 (0.98–1.11)	0.22	-	-
Pre-ECMO renal replacement therapy	2.13 (0.61–7.46)	0.24	-	-
Pre-ECMO prone positioning	0.58 (0.21–1.59)	0.29	-	-
Pre-ECMO inhaled nitric oxide	4.55 (1.37–15.11)	0.01	7.96 (1.58–40.06)	0.01
Pre-ECMO dynamic driving pressure	1.11 (0.999–1.23)	0.051	-	-
Pre-ECMO respiratory rate	1.04 (0.97–1.12)	0.29	-	-
Pre-ECMO PaO ₂ /FiO ₂	1.01 (0.99–1.02)	0.31	-	-
Extended ECMO use	0.23 (0.06–0.93)	0.04	0.10 (0.02–0.64)	0.02

*Variables with p-values of <0.20 in the univariate analysis were included in the multivariate analysis by using stepwise backward selection procedures.

OR: odds ratio; CI: confidence interval; APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit; ECMO: extracorporeal membrane oxygenation; PaO₂: arterial oxygen tension; FiO₂: fraction of inspired oxygen.

Table 4. Cox proportional hazards regression model with 60-day mortality as outcome

Variable	Unadjusted HR (95% CI)	p-value	Adjusted HR* (95% CI)	p-value
Male sex	0.56 (0.26–1.21)	0.14	-	-
APACHE II score at ICU admission	1.03 (0.99–1.07)	0.20	-	-
Pre-ECMO renal replacement therapy	1.84 (0.81–4.16)	0.14	-	-
Pre-ECMO prone positioning	0.62 (0.29–1.31)	0.21	-	-
Pre-ECMO inhaled nitric oxide	3.24 (1.55–6.77)	0.002	4.19 (1.87–9.36)	<0.001
Pre-ECMO bicarbonate infusion	1.72 (0.70–4.23)	0.24	-	-
Pre-ECMO dynamic driving pressure	1.07 (1.003–1.13)	0.04	-	-
Pre-ECMO respiratory rate	1.03 (0.97–1.09)	0.28	-	-
Pre-ECMO PaO ₂ /FiO ₂	1.01 (0.999–1.02)	0.09	1.01 (1.01–1.02)	0.001
Extended ECMO use	0.36 (0.11–1.18)	0.09	0.19 (0.06–0.66)	0.009

*Variables with p-values of <0.20 were included in the multivariate analysis using stepwise backward selection procedures.

HR: hazard ratio; CI: confidence interval; APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit; ECMO: extracorporeal membrane oxygenation; PaO₂: arterial oxygen tension; FiO₂: fraction of inspired oxygen.

these “protective” mechanical ventilation strategies may not be possible. In addition, even if the above-mentioned variables are kept within the defined limits, the patient might not be ventilated in a lung protective manner^{11,12}. Rescue therapies such as ECMO may be used timely or even immediately to resolve potentially deleterious conditions, although defined thresholds of mechanical ventilation that characterize the status under which the therapy is to be applied are required. However, a clear cutoff that defines severe or life-threatening hypoxemia is still an ongoing matter of debate¹⁹, and evidence supporting indications or contraindications to ECMO initia-

tion in ARDS is scarce. A recent international multicenter randomized ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial tested the efficacy of early venovenous-ECMO in patients with severe ARDS with conventional mechanical ventilation with prone positioning²⁰. The analysis of the primary end point (60-day mortality) showed no significant benefit of early ECMO, although the 28% rate of crossover to ECMO among patients with refractory hypoxemia in the conventional group (43% of them survived) may have diluted the potential effect of ECMO. Meanwhile, patients who were enrolled in this trial were very hypoxemic (PaO₂/FiO₂ ratio <80)

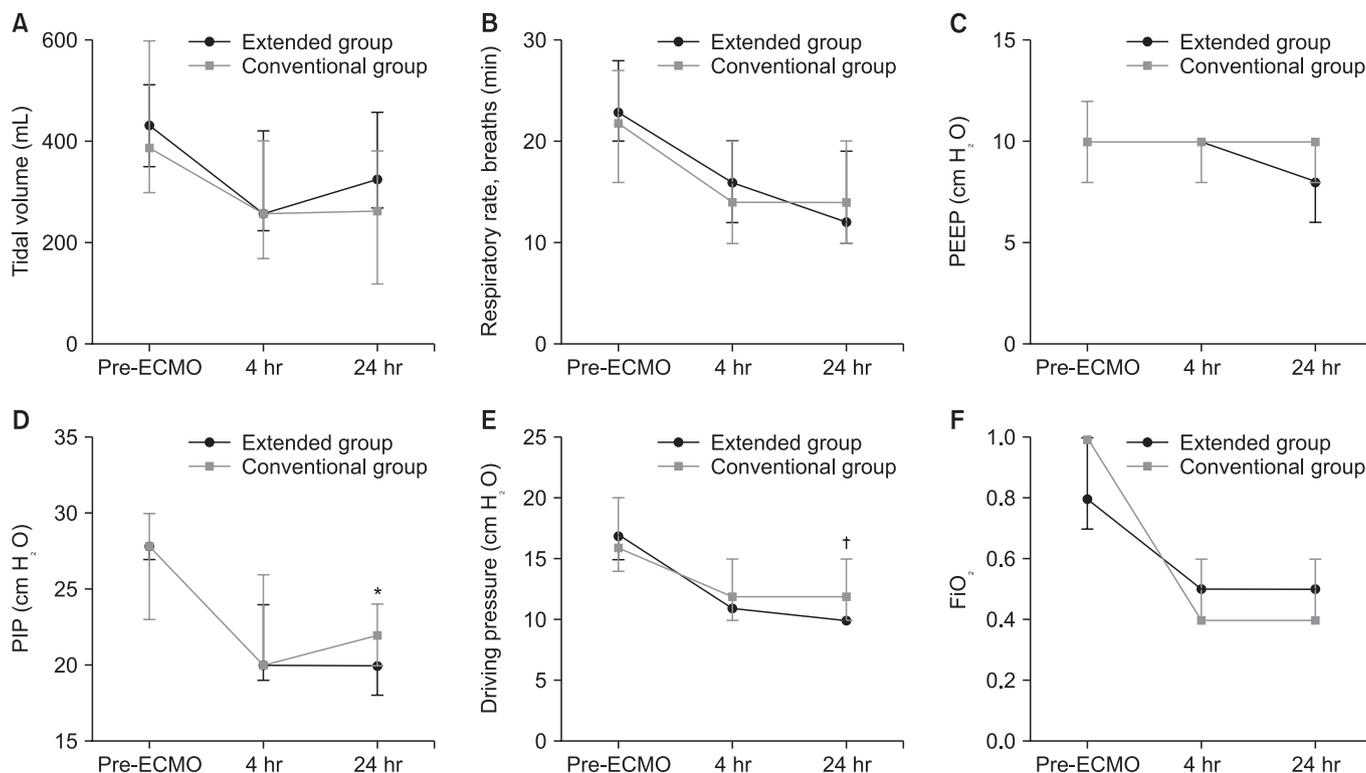


Figure 3. Serial changes in tidal volume (A), respiratory rate (B), positive end-expiratory pressure (PEEP) (C), peak inspiratory pressure (PIP) (D), dynamic driving pressure (E), and fraction of inspired oxygen (FiO₂) (F) in the extended group (dark line) and the conventional group (gray line) during the 24-hour study period. Data is presented as a median value (interquartile range). **p*<0.05. †*p*=0.13. ECMO: extracorporeal membrane oxygenation.

and the trial did not evaluate patients with less severe forms of ARDS.

The use of ECMO in ARDS patients with less severe hypoxemia may be beneficial for the following reasons. First, venovenous-ECMO with an “ultraprotective” mechanical ventilation strategy (tidal volume reduction to below 6 ml/kg of predicted body weight to achieve a plateau pressure less than 25 cm H₂O) may further reduce VILI and mortality in patients mechanically ventilated for ARDS^{21,22}. In addition, venovenous-ECMO may reduce the effect of acute lung injury on right ventricular dysfunction by reducing hypoxic pulmonary vasoconstriction and unloading the right ventricle²³. Second, modern ECMO devices are simpler, safer, and require less anticoagulation and it is now possible to support patients for weeks²⁴. Third, patients with ECMO can be awake, facilitating rehabilitation and decreasing weakness and deconditioning. Several studies indicate that early rehabilitation in ECMO patients may improve survival, reduce mechanical ventilation duration, shorten ICU length of stay, and improve functional recovery^{25,26}. Fourth, ECMO might improve long-term quality-of-life by improving blood oxygenation in severely hypoxemic ARDS patients. In fact, ARDS patients treated with ECMO^{3,15} showed comparable or better health-related quality-of-

life scores than patients with less severe ARDS treated with conventional management²⁷. Lastly, several studies have identified duration of mechanical ventilation prior to ECMO initiation and low pre-ECMO respiratory system compliance as factors strongly associated with mortality in severe ARDS patients receiving ECMO^{15,16,28}.

Several studies have described the impact of different ventilator settings in ARDS patients undergoing ECMO^{17,22,28}, with lower PEEP levels and higher driving pressure independently associated with mortality. In this study, we observed changes in ventilator settings within 24 hours of ECMO initiation. Thus, the extended group had lower peak inspiratory pressure and dynamic driving pressure after 24-hour ECMO support. We used the difference between the peak inspiratory pressure and PEEP to calculate the “dynamic” driving pressure¹⁷ because most patients were on pressure-controlled ventilation during the evaluation of ventilator settings. Moreover, our multivariate logistic regression and Cox proportional hazards modeling demonstrated that the extended group was independently associated with 60-day survival. Based on our findings, implementation of ECMO with extended indications accompanied by protective ventilation settings may affect the clinical outcome in ARDS patients.

This multicenter study had several limitations of note. First, the study was retrospective and underpowered. Its non-randomized design was prone to selection bias and precluded any inference of causality regarding the association between extended ECMO use and outcome. We also could not adjust for unmeasured confounders, and a matching process between the two groups was not feasible due to a relatively small sample size used for the extended group compared with that of conventional group. In addition, the multiple confounding factors may have affected the clinical outcome, despite the similar baseline characteristics of the study patients in the extended and conventional groups. Second, one could argue that the better outcomes in the extended group could have been related with the better oxygenation status of patients, considering that several studies identified oxygenation criteria as a predictor of mortality in ARDS^{2,29}. However, the multivariate analysis showed no relation between PaO₂/FiO₂ ratio and mortality. The Cox regression analysis even showed a positive association between increased PaO₂/FiO₂ ratio and mortality, although it is difficult to explain such a phenomenon. Moreover, pre-ECMO ventilator settings in the extended group were comparable to those in the conventional group, and most patients in the extended group had already been managed with other rescue therapies before ECMO initiation. Third, ventilator settings were collected only at baseline, 4 hours, and 24 hours after ECMO application. We do not know if specific ventilator strategies after day 1 would have changed the patient outcomes. Lastly, criteria for assessing ECMO for ARDS, mechanical ventilation on ECMO, and weaning from ECMO were not standardized among centers. In addition, there was a lack of data on some of the treatment modalities (level of sedation, ECMO settings, anticoagulation, transfusion, or rehabilitation) and complications (either directly related to the ECMO circuit or patient-related) because these data were not collected due to the purposes of the initial cohort. It remains possible that the two groups were not similarly treated, and this may have affected the treatment outcome.

In conclusion, our comparison of extended indications of ECMO implementation with conventional indications suggests that extended ECMO use accompanied by protective ventilation strategies may improve the clinical outcome for patients with ARDS.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Material

Supplementary material can be found in the journal homepage (<http://www.e-trd.org>).

Supplementary Table S1. Changes in ventilator settings between the extended group and the conventional group during the 24-hour study period.

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Supplementary Table S1. Changes in ventilator settings between the extended group and the conventional group during the 24-hour study period

Variable	Extended group (n=14)	Conventional group (n=48)	p-value
Pre-ECMO			
Positive end-expiratory pressure, cm H ₂ O	10 (10–12)	10 (8–12)	0.60
Peak inspiratory pressure, cm H ₂ O	28 (27–30)	28 (23–30)	0.67
Dynamic driving pressure, cm H ₂ O	17 (15–20)	16 (14–20)	0.58
Tidal volume, mL	436 (350–512)	390 (300–600)	0.83
Respiratory rate, breaths/min	23 (20–28)	22 (16–27)	0.37
FiO ₂	0.8 (0.7–1.0)	1.0 (1.0–1.0)	<0.001
4 Hours			
Positive end-expiratory pressure, cm H ₂ O	10 (8–10)	10 (8–10)	0.93
Peak inspiratory pressure, cm H ₂ O	20 (19–24)	20 (20–26)	0.46
Dynamic driving pressure, cm H ₂ O	11 (10–15)	12 (10–15)	0.58
Tidal volume, mL	256 (225–421)	258 (170–400)	0.55
Respiratory rate, breaths/min	16 (12–20)	14 (11–19)	0.24
FiO ₂	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.81
24 Hours			
Positive end-expiratory pressure, cm H ₂ O	8 (6–10)	10 (8–10)	0.051
Peak inspiratory pressure, cm H ₂ O	20 (18–20)	22 (20–24)	0.006
Dynamic driving pressure, cm H ₂ O	10 (10–12)	12 (10–15)	0.13
Tidal volume, mL	325 (270–458)	264 (120–380)	0.21
Respiratory rate, breaths/min	12 (12–19)	14 (10–20)	0.92
FiO ₂	0.5 (0.4–0.5)	0.4 (0.4–0.6)	0.66

Values are presented as median (interquartile range).

ECMO: extracorporeal membrane oxygenation; FiO₂: fraction of inspired oxygen.