

# Extracorporeal Membrane Oxygenation versus Conventional Ventilator Support in COVID-19 Patients with Acute Respiratory Distress Syndrome

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**Background:** Acute respiratory distress syndrome (ARDS) is an undesirable outcome of severe coronavirus disease 2019 (COVID-19). Although venovenous extracorporeal membrane oxygenation (VV-ECMO) has been widely accepted as a rescue therapy for severe ARDS, its use in COVID-19-associated ARDS is still debated.

**Objective:** To compare the clinical outcomes of COVID-19 patients treated with VV-ECMO or conventional ventilator support.

**Materials and Methods:** The authors conducted a retrospective study in Bangkok Heart Hospital, Thailand, between March and September 2021. Patients were divided into ECMO and non-ECMO or conventional ventilator support groups. The primary outcome was in-hospital mortality, and the secondary outcomes were complications, length of ICU stay, recovery time after extubation, and total length of hospital stay.

**Results:** Of the 3,053 COVID-19 patients, 36 (1.18%) developed severe ARDS, which 12 were treated with VV-ECMO and 24 with a conventional ventilator. In-hospital mortality was non-significantly lower in the ECMO group at 58.3% versus 83.3% ( $p=0.126$ ). Upper gastrointestinal bleeding was non-significantly more common in the ECMO group at 41.7% versus 25.0% ( $p=0.306$ ) but there were no cases of deep vein thrombosis in the ECMO group at 0% versus 20.8% ( $p=0.088$ ). There were no significant differences in any other complications. Six patients, including four in the ECMO group and two in the non-ECMO group underwent cytokine removal via HA330 hemoperfusion, but interleukin-6 did not decrease in these patients.

**Conclusion:** VV-ECMO in COVID-19-associated ARDS patients did not significantly decrease mortality compared to conventional ventilator therapy. A multidisciplinary team should develop an optimal treatment plan for each COVID-19-associated ARDS patient.

**Keywords:** SARS-CoV-2; Intensive care unit, Artificial respiration

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The spreading of coronavirus disease 2019 (COVID-19) first emerged in early December 2019 in Wuhan, China<sup>(1)</sup>. On January 12, 2020, Thailand was the first country to announce the detection of COVID-19 outside the epidemic area.

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The pandemic was officially declared on March 11, 2020, by The World Health Organization<sup>(2)</sup>. In most studies, the mortality rate ranged from 0.4% to 19.62%<sup>(3)</sup>, depending on the COVID-19 variant. Acute respiratory distress syndrome (ARDS) was found in up to 3.6% of COVID-19 patients according to the Polish National Hospital Register, and the mortality rate among these patients was 88.8%<sup>(4)</sup>.

The use of extracorporeal membrane oxygenation (ECMO) was dramatically increased after the publication of The Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial<sup>(5)</sup>. Although venovenous ECMO (VV-ECMO) has been widely accepted as a rescue therapy for severe ARDS<sup>(6)</sup>, its benefit in severe COVID-19-associated ARDS (C-ARDS) compared to conventional ventilation is still debated. The

mortality rate among C-ARDS patients after ECMO was reported to increase from 38% before May 1, 2020, to 53% between May 1 and May 31, 2020, and then to 59% after May 31, 2020, according to the international Extracorporeal Life Support Organization Registry<sup>(7)</sup>.

The decision whether to use VV-ECMO in C-ARDS patients remains a challenge. The present study aimed to compare the in-hospital mortality, complications, length of ICU stay, recovery time after extubation, and total length of hospital stay among severe C-ARDS patients treated by VV-ECMO (ECMO group) and the conventional ventilation therapy (non-ECMO group). The authors hypothesized that VV-ECMO would be associated with better outcomes.

## Materials and Methods

The authors conducted a retrospective observational study in Bangkok Heart Hospital, Bangkok, Thailand, between March 1 and September 30, 2021. The present study was granted ethical approval by the Bangkok Hospital Institutional Review Board (COA 2022-01).

## Patients

Based on the US National Institutes of Health (NIH) treatment guidelines for confirmed severe acute respiratory syndrome coronavirus (SARS-CoV)-2 infection<sup>(8)</sup>, severe illness was defined as oxygen saturation on room air to less than 94%, partial pressure of oxygen (PaO<sub>2</sub>)/fraction of inspired oxygen (FiO<sub>2</sub>) at less than 300 mmHg, respiratory rate of more than 30 breaths/minute, or lung infiltration of more than 50% on imaging. All COVID-19 patients with respiratory failure who needed intubation were transferred to an intensive care unit (ICU). Chest physicians managed the ventilator adjustment and respiratory care using a lung-protective ventilation strategy.

Patients with PaO<sub>2</sub>/FiO<sub>2</sub> of less than 150 mmHg were placed in prone positions after ventilator settings were optimized, with high positive end-expiratory pressure (PEEP). In some patients, a synthetic analog of prostacyclin PGL<sub>2</sub> (iloprost) was also prescribed as an inhaled pulmonary vasodilator.

The authors followed the ECMO treatment guidelines for COVID-19 patients from the Extracorporeal Life Support Organization (ELSO)<sup>(9)</sup>. The indications for VV-ECMO included PaO<sub>2</sub>/FiO<sub>2</sub> of less than 80 mmHg for more than six hours, or less than 50 mmHg for more than three hours, or

pH of less than 7.25 with partial pressure of carbon dioxide (PaCO<sub>2</sub>) of 60 mmHg or more for more than six hours. A multidisciplinary team of cardiothoracic surgeons and chest physicians made a final decision after assessing the patient comorbidities and financial status.

Cytokine removal using HA330 resin cartridges was also conducted in patients with acute kidney injury undergoing continuous hemofiltration.

## VV-ECMO protocol

Ultrasonography-guided cannulation for VV-ECMO was conducted in every case. In general, the inflow (drainage) cannula was inserted at the right common femoral vein. The outflow (return) cannula was placed at the right internal jugular vein to reach the normal VV-ECMO position. The authors used a Getinge (Rastatt, Germany) Rotaflow® I system and a Getinge Cardiohelp® ECMO system. Heparin was infused to maintain an activated partial thromboplastin time (APTT) ratio of 1.3 to 1.5 when there were no contraindications to anti-coagulant use. The ECMO flow was set at 3.0 to 3.5 times the patient's cardiac index as measured in L/minute/m<sup>2</sup>.

## Outcomes

The primary outcome was in-hospital mortality. The secondary outcomes were complications including acute kidney injury, sepsis, pulmonary embolism, thrombosis, upper gastrointestinal bleeding, stroke, pneumothorax, deep vein thrombosis, and thrombocytopenia, length of ICU stay, recovery time after extubation, and total length of hospital stay.

## Statistical analysis

Continuous data were examined for normal distribution using the Shapiro-Wilk test. Normally distributed data were expressed as mean ± standard deviation or median (interquartile range) when non-normally distributed. Normally distributed data were compared between the two groups by Student's t-test and non-normally distributed data were compared using the Mann-Whitney U test. Categorical data were expressed as the absolute number (percentage) and compared between the two groups by the chi-square test or Fisher's exact test as appropriate. A p-value less than or equal 0.05 was considered statistically significant. The data were analyzed using IBM SPSS Statistics, version 23 (IBM Corp., Armonk, NY, USA).

## Results

Of the 3,053 patients diagnosed with COVID-19 admitted during the observational period, 64 needed ventilator support, and 36 patients (1.18%) later developed severe ARDS with PaO<sub>2</sub>/FiO<sub>2</sub> of less than 80 in most cases. Of these 36 patients, 12 (33.33%) were treated with ECMO (ECMO group) and 24 (66.67%) with a conventional ventilator (non-ECMO group). The ventilator settings in these two groups involved a lung-protective strategy, with prone positioning when appropriate.

Regarding the baseline characteristics (Table 1), the patients were significantly younger in the ECMO group than the non-ECMO group at 48.9±11.7 versus 74.7±11.5 years (p<0.001). The mean PaO<sub>2</sub>/FiO<sub>2</sub> was 46.4±6.0 in the ECMO group versus 50.1±7.7 in the non-ECMO group (p=0.129). Coronary artery disease was significantly less common in the ECMO group than the non-ECMO group with 0 (0%) versus 9 (37.5%) (p=0.014). Cardiomyopathy was non-significantly less common in the ECMO group than the non-ECMO group with 1 (8.3%) versus 4 (16.7%) (p=0.496). There were also no significant differences between the groups regarding gender, left ventricular ejection, or other underlying diseases.

Regarding adjunctive therapy (Table 2), inhaled pulmonary vasodilators were prescribed for nine patients (37.5%) in the non-ECMO group, but none in the ECMO group (p=0.014). Vasopressors were given to all patients in both groups, based on hemodynamic status. Prone positioning was not significantly different between the ECMO and the non-ECMO groups with 7 (58.3%) versus 16 (66.7%) (p=0.624). Pre-treatment PaO<sub>2</sub> was non-significantly lower in the ECMO group than the non-ECMO group at 46.4±6.1 versus 47.8±8.3 (p=0.589) (Table 2). For patients in the ECMO group, the mean PaO<sub>2</sub> increased to 201.8±27.6 mmHg after ECMO establishment, and the mean PaCO<sub>2</sub> decreased to 27.6±8.0 mmHg.

In-hospital mortality was non-significantly lower in the ECMO group than the non-ECMO group at 58.3% versus 83.3% (p=0.126) (Table 3). All causes of death were from severe respiratory failure in both groups. Overall, the length of ICU stay was 29±19 days in the ECMO group versus 21±14 days in the non-ECMO group (p=0.192). In surviving patients, the length of ICU stay was 34.20±26.97 days in the ECMO group versus 25.75±29.11 days in the non-ECMO group, (p=0.665). After extubation, the recovery time was 15 (43) days in the ECMO group versus 33.25 (1) days in the non-ECMO group, (p=0.325). The total length of hospital stay was 33±22

**Table 1.** Baseline demographic and clinical characteristics

Variable	ECMO (n=12)	Non-ECMO (n=24)	p-value
Age (year); mean±SD	48.9±11.7	74.7±11.5	<0.001*
Body mass index (kg/m <sup>2</sup> ); mean±SD	27.6±6.6	27.2±4.3	0.793
Sex; n (%)			
Male	8 (66.7)	12 (50.0)	0.343
Female	4 (33.3)	12 (50.0)	
PaO <sub>2</sub> /FiO <sub>2</sub> ; mean±SD	46.4±6.0	50.1±7.7	0.129
LVEF (%); mean±SD	66.4±16.2	63.7±18.8	0.774
Cardiomyopathy; n (%)	1 (8.3)	4 (16.7)	0.496
Underlying condition; n (%)			
Obesity	4 (33.3)	5 (20.8)	0.414
Hypertension	7 (58.3)	18 (75.0)	0.306
Diabetes	4 (33.3)	14 (58.3)	0.157
Hyperlipidemia	3 (25.0)	11 (45.8)	0.227
Asthma/chronic obstructive pulmonary disease	0 (0.0)	2 (8.3)	0.303
Coronary artery disease	0 (0.0)	9 (37.5)	0.014*
Chronic kidney disease	1 (8.3)	0 (0.0)	0.151
Obstructive sleep apnea	2 (16.7)	1 (4.2)	0.201
Gout	1 (8.3)	0 (0.0)	0.151
Cancer	0 (0.0)	3 (12.5)	0.201
Cerebrovascular accident	0 (0.0)	5 (20.8)	0.088

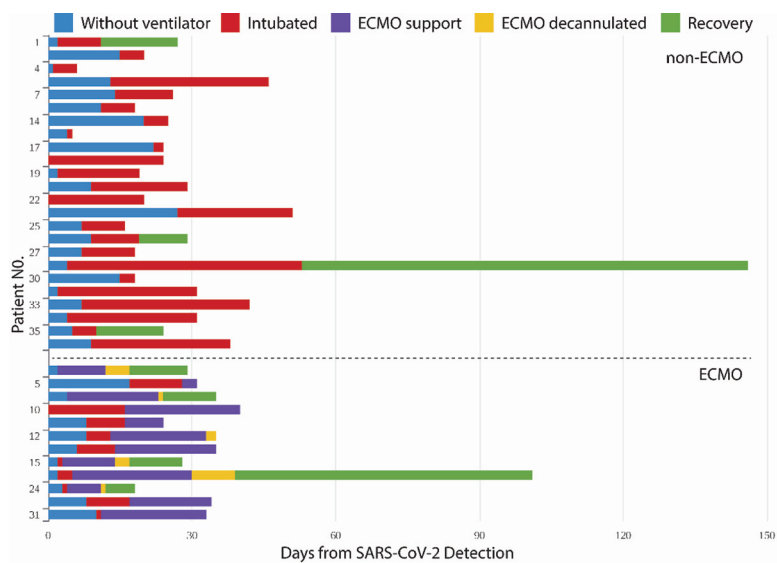
ECMO=extracorporeal membrane oxygenation; FiO<sub>2</sub>=fraction of inspired oxygen; LVEF=left ventricular ejection fraction; PaO<sub>2</sub>=partial pressure of oxygen; SD=standard deviation

**Table 2.** Clinical characteristics

Variable	ECMO (n=12)	Non-ECMO (n=24)	p-value
Ventilation parameter; mean±SD			
FiO <sub>2</sub>	100±0	96.0±11	0.084
PEEP (cmH <sub>2</sub> O)	11±2	11±3	0.817
Respiration rate (bpm)	19±4	21±7	0.268
Tidal volume (mL)	373±101	444±138	0.130
Peak inspiratory pressure (cmH <sub>2</sub> O)	28.1±3.6	26.7±7.5	0.479
Plateau pressure (cmH <sub>2</sub> O)	19.7±2.5	18.7±5.3	0.479
Baseline arterial blood gas; mean±SD			
pH	7.35±0.11	7.30±0.14	0.226
PaCO <sub>2</sub> (mmHg)	47.3±9.2	62.6±33.8	0.046*
PaO <sub>2</sub> (mmHg)	46.4±6.1	47.8±8.3	0.589
Bicarbonate	26.5±3.7	29.7±9.6	0.161
Adjunctive therapy; n (%)			
Inhaled pulmonary vasodilators	0 (0.0)	9 (37.5)	0.014*
Vasopressors	12 (100)	24 (100)	N/A
Prone positioning	7 (58.3)	16 (66.7)	0.624

ECMO=extracorporeal membrane oxygenation; FiO<sub>2</sub>=fraction of inspired oxygen; PEEP=positive end-expiratory pressure; PaCO<sub>2</sub>=partial pressure of carbon dioxide; SD=standard deviation

days in the ECMO group versus 30±27 days in the non-ECMO group, (p=0.794). The treatment duration



**Figure 1.** Treatment duration. Intervention timing for each patient from symptoms without ventilation support to the end result period. Upper part: non-ECMO group; lower part: ECMO group.

**Table 3.** Outcomes

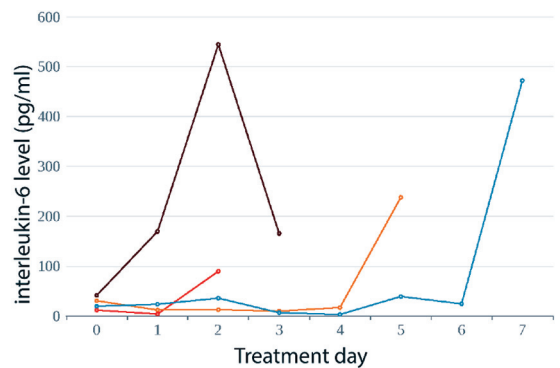
Variable	ECMO (n=12)	Non-ECMO (n=24)	p-value
Complication; n (%)			
Acute kidney injury	1 (8.3)	6 (25)	0.234
Sepsis	4 (33.3)	11 (45.8)	0.238
Pulmonary embolism	2 (16.7)	1 (4.2)	0.201
Thrombosis	1 (8.3)	7 (29.2)	0.156
Upper gastrointestinal bleeding	5 (41.7)	6 (25.0)	0.306
Stroke	0 (0.0)	1 (4.2)	0.473
Pneumothorax	3 (25.0)	3 (12.5)	0.343
Deep vein thrombosis	0 (0.0)	5 (20.8)	0.088
Thrombocytopenia	2 (16.7)	1 (4.2)	0.201
Length of ICU stay (days); mean±SD	29±19	21±14	0.192
Length of stay (days); mean±SD	33±22	30±27	0.794
In-hospital mortality; n (%)	7 (58.3)	20 (83.3)	0.126
Recovery time after extubation (days); median [IQR]	15 [43]	33.25 [1]	0.325

ECMO=extracorporeal membrane oxygenation; ICU=intensive care unit; IQR=interquartile range; SD=standard deviation

for each patient is shown in Figure 1.

The complications did not significantly differ between the two groups (Table 3). Upper gastrointestinal bleeding was non-significantly more common in the ECMO group at 41.7% versus 25.0% ( $p=0.306$ ), but this was not a leading cause of death. Deep vein thrombosis was non-significantly more common in the non-ECMO group at 20.8%, with zero cases in the ECMO group, ( $p=0.088$ ).

Cytokine removal at two hours per session each day and a mean treatment course of three days



**Figure 2.** Interleukin-6 level after cytokine removal (2 hours/session each day for a range of 2 to 7 days) via HA330 hemoperfusion during continuous hemofiltration. Post-treatment interleukin-6 level did not exhibit the predicted decreases. (The interleukin-6 level of the individual patient showed in a separate line)

during continuous hemofiltration was performed in six patients including four in the ECMO group and two in the non-ECMO group. The pre- and post-treatment interleukin-6 (IL-6) levels are shown in Figure 2. The post-treatment IL-6 levels did not exhibit the predicted dramatic decreases. Only one patient survived in the ECMO group, and none in the non-ECMO group.

## Discussion

At the beginning of the COVID-19 pandemic, the decision regarding whether to use VV-ECMO in

patients with severe ARDS was difficult. The decision to establish the VV-ECMO in COVID-19 patients strongly followed the guideline from ELSO<sup>(9)</sup>. After initiating VV-ECMO, the present study in-hospital mortality was non-significantly lower in the ECMO group than in the non-ECMO group at 58.3% versus 83.3%. A study in expert European ECMO centers showed that with experience and restricted indications, in-hospital mortality could be reduced to 25.6%, with good clinical outcomes<sup>(10)</sup>.

Appropriate timing of VV-ECMO and adjunctive procedures such as lung-protective ventilation strategy, and in particular, prone positioning are also important. In the P<sub>RO</sub>VENT-COVID study, prone positioning reduced the mortality rate from 51.7% to 42.0% ( $p=0.02$ ) in indicated patients<sup>(11)</sup>. In addition, prone positioning among C-ARDS patients, like in patients with non-COVID ARDS, effectively improved ventilation parameters<sup>(12)</sup>. Nevertheless, prolonged prone positioning can lead to complications. Therefore, a multidisciplinary team should develop an appropriate strategy for each patient. Based on the authors' experience, they recommend that prone positioning should not be delayed in C-ARDS patients.

Around a third of the present study patients had upper gastrointestinal bleeding. Most of the patients with this condition did not receive anticoagulants during the VV-ECMO supportive period. Alexey et al. found that platelet depletion was present in COVID-19 patients with ECMO<sup>(13)</sup>, and 16.7% of the present study VV-ECMO patients also developed thrombocytopenia. This indicates that heparin should be used with caution in COVID-19 patients. On the other side, the incidence of deep vein thrombosis in the VV-ECMO group was significantly lower compared to the non-ECMO group, which may result from continuous heparin infusion to prevent blood clot formation in the ECMO circuit.

Cytokine removal via HA330 hemoperfusion during continuous hemofiltration did not improve survival in the present study. Likewise, Kacar et al.<sup>(14)</sup> reported that the use of HA330 had no impact on the prognosis of septic shock patients in an ICU setting. However, recent research in COVID-19 patients found that continuous treatment with other absorbents such as CytoSorb® for 72 hours significantly reduced inflammatory biomarkers<sup>(15)</sup> and significantly decreased in-hospital mortality from 33.7% to 26.9%<sup>(16)</sup>.

One of the present study patients had a cardiac arrest due to severe hypoxia and underwent VV-

ECMO. He had no neurological response after VV-ECMO initiation. Later, brain computed tomography showed a large infarction area, indicating that brain death had occurred. Based on this situation, the authors do not recommend immediate VV-ECMO initiation in patients with cardiac arrest during pandemic situations unless brain imaging is evaluated.

The patients in the ECMO group were significantly younger than in the non-ECMO group. This may be one factor underlying the non-significantly lower mortality rate in this group. A study conducted at U.S. academic centers reported that in-hospital mortality increased with age in COVID-19 patients treated with ECMO. The mortality rate was 73.7% in patients aged 65 years or older<sup>(17)</sup>. Therefore, VV-ECMO should be considered in patients younger than 65 years with well-controlled comorbidities.

The present study retrospective study had limitations. First, the sample size was low due to the hospital's low incidence of severe ARDS. Second, the indications for VV-ECMO in COVID-19 patients varied over time during the present study timeframe. Third, further investigations should explore the effects of HA330 hemoperfusion on inflammatory biomarkers other than IL-6 such as C-reactive protein, D-dimer, ferritin, and IL-10.

In conclusions, VV-ECMO compared to conventional ventilator therapy non-significantly lowered the in-hospital mortality rate in selected C-ARDS patients. Further research is needed to determine whether VV-ECMO is beneficial and cost-effective for C-ARDS patients, particularly for patients younger than 65 years with well-controlled comorbidities. In clinical settings, a multidisciplinary team should develop a specific treatment plan for each patient.

### **What is already known on this topic?**

ECMO has been accepted as a treatment to rescue patients with severe ARDS when combined with the appropriate modalities such as prone position and adequate protective ventilation strategy. However, in severe COVID-19 infection patients with respiratory failure, the benefit of ECMO is still doubtful.

### **What this study adds?**

VV-ECMO compared to conventional ventilator therapy is non-significantly lowered the in-hospital mortality rate in selected C-ARDS patients. Further research is needed to determine whether VV-ECMO

is beneficial and cost-effective for C-ARDS patients, particularly for patients younger than 65 years with well-controlled comorbidities. In clinical settings, a multidisciplinary team should develop a specific treatment plan for each patient.

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### Conflicts of interest

The authors declare no conflict of interest.

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