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SHORT REVIEW

Extracorporeal membrane oxygenation (ECMO) for COVID-19 patients

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ABSTRACT:

During the current outbreak of coronavirus disease 2019 (COVID-19), Extracorporeal Membrane Oxygenation (ECMO) support could be considered as the rescue treatment from life threatening condition among severe COVID-19 patients who did not respond to mechanical ventilation. We propose that veno-venous ECMO should be considered if patient has persistence PaO2:FiO2 ratio lower than 100 mmHg after appropriate mechanical ventilator adjustment, muscle relaxant and prone position. During ECMO support, treatment against cytokine storm, including non-selective immune suppression with systemic steroid, or selective interleukin-6 inhibition and Janus Kinase inhibition should be considered. Heparin infusion is still the recommended anticoagulant to maintain activated partial thromboplastin time (APTT) ratio range 1.5-2.0. The overall hospital mortality was comparable with respiratory failure patients, requiring ECMO support from other causes, which was reported about 37-50%. The decision to initiate ECMO could be depended on the individual hospital capacity and treatment availability. Contact for transfer a candidate ECMO patient to an ECMO center is also an alternative option.

Keywords: Extracorporeal membrane oxygenation, ECMO, Veno-venous (VV) ECMO, COVID-19, Acute respiratory distress syndrome, ARDS, Refractory hypoxemia

Introduction

During the current outbreak of coronavirus disease 2019 (COVID-19), more than one hundred and seventy million people worldwide were infected. Up to 15% of COVID-19 patients developed acute respiratory distress syndrome (ARDS)[1]. Although most of them were successfully treated with conventional mechanical ventilation with optimal positive end expiratory pressure (PEEP) and low tidal volume strategy, a significant proportion of patients did not respond to those recommended treatment. Extracorporeal Membrane Oxygenation (ECMO) had been used as a rescue therapy for ARDS patient with refractory hypoxemia despite receiving high setting mechanical ventilation support [2,3]. In the EOLIA trial, moderate to severe ARDS patients with refractory hypoxemia or severe respiratory acidosis after optimization of mechanical ventilator settings had the treatment benefit of V-V ECMO [4]. Hence, for severe COVID-19 patients who did not respond to mechanical ventilation, ECMO support could be considered as the rescue treatment from life threatening condition. The basic mechanisms of ECMO for treatment rescue in COVID-19 ARDS could be comparable with those ARDS from other causes. During ECMO support, it allows the patients to be ventilated with lower tidal volume, lower inspiratory pressure and lower fraction of inspiratory oxygen. This resulted in prevention of barotrauma, volutrauma, atelectrauma and oxygen toxicity among ARDS patients who receiving ECMO support.

Current situation of ECMO support in Thailand, there were several referral centers, included University affiliate hospital, Government hospital and Private Hospital, that established ECMO support service with reported impressive patients' outcome [5-10]. Then ECMO support should be considered as lifesaving procedure for severe COVID-19 patients who refractory for conventional mechanical ventilator support. This article aims

to summarize the indication, special consideration and outcome of ECMO support among COVID-19 patients.

Indication of ECMO support in COVID-19 patients

ECMO support should be initiated for COVID patients who did not respond to conventional treatment. Veno-venous (VV) ECMO is mainly used in COVID patients with refractory hypoxemia, except in a few cases, who's complicated with severe impaired hemodynamic status with low cardiac output, then veno-arterial (VA) ECMO should be considered. According to Extracorporeal Membrane Oxygenation for COVID-19: Updated 2021 Guidelines from the Extracorporeal Life Support Organization (ELSO), patients who has PaO_2:FiO_2 ratio lower than 150 mmHg should be treated by high PEEP titration, low tidal volume strategy, neuromuscular blocking agent and appropriate sedation [11]. Prone position should be performed, if there is no contraindication. Recruitment maneuver could be considered among refractory hypoxemic due to severe COVID-19 pneumonia patients before initiate ECMO. However, this should be performed under closed monitoring, in view of the potential association of recruitment maneuver and detrimental effects to patients with moderate to severe ARDS from other causes [12]. Patients who do not respond to those mentioned treatment which defined by PaO_2:FiO_2 ratio lower than 80 mmHg for at least 6 hours or lower than 50 mmHg for at least 3 hours should be initiated ECMO. Patient who has severe respiratory acidosis with pH lower than 7.25 with $PaCO_2$ higher than 60 mmHg for more than 6 hours would be the candidate for ECMO support. In our experience, considering about time consuming during personal protection equipment (PPE) wearing before performing ECMO cannulation procedure and our ECMO cohort result which identified the association of low PaO_2:FiO_2 ratio before ECMO initiation and poor ECMO outcome, we consider persistence PaO_2:FiO_2 ratio lower than 100 mmHg after prone position as the indication for ECMO initiation (Figure 1). In a situation of insufficient resources such as medical personnel or equipment, the early consideration for ECMO support would allow adequate timing to contact for transfer a candidate patient to ECMO center, in case there is no ECMO available onsite.

KEY MESSAGES:

- ECMO support could be considered as a lifesaving procedure for severe COVID 19 patients who did not respond to mechanical ventilator support, despite receiving optimal PEEP titration, neuromuscular blocking agent and prone positioning.
- The overall hospital survival rate of ECMO support for COVID patients was comparable with respiratory failure requiring ECMO support from other causes.
- In a situation of no ECMO available onsite, the early consideration for ECMO support would allow adequate timing to contact for transfer a candidate patient to ECMO center.

Concerning about resource limitation during COVID-19 pandemic era and low probability of survival among poor prognosis patients, ECMO should not be initiated in patient with advance age, clinical frailty, advance stage malignancy, uncontrolled bleeding and multiple organs dysfunction with no plan of long-term treatment [11]. Prolong mechanical ventilator more than 10 days should be considered as a contraindication, according to ELSO 2021 guideline.

Special consideration of ECMO support in COVID-19 patients

Severe COVID-19 cases had typical feature of cytokine storm, life-threatening systemic inflammatory syndromes involving elevated levels of circulating cytokines and immune-cell hyperactivation. The result of overwhelming immune respond causes vasodilatory shock, vascular leakage syndrome, disseminated coagulopathy (DIC), vascular occlusion and bleeding complication. In severe case, multiple organ dysfunction, which included acute respiratory distress syndrome,

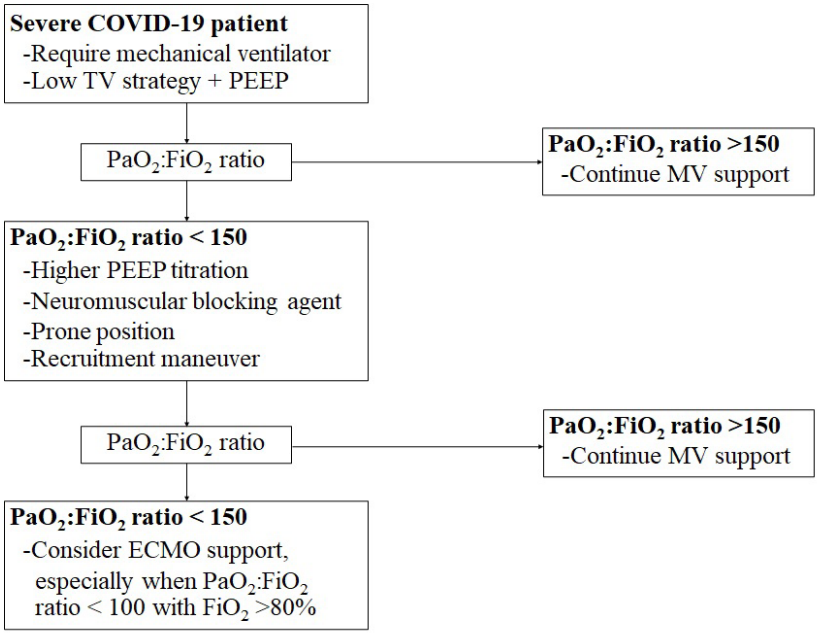

Figure 1. Flow diagram for management of severe COVID-19 patient with severe hypoxemia, requiring mechanical ventilator and considering as a candidate for ECMO support.
Abbreviation: TV; tidal volume, PEEP; positive end expiratory pressure, MV; mechanical ventilator, ECMO; extracorporeal membrane oxygenation

acute renal failure, and cardiomyopathy can occurred. Most of COVID-19 ECMO candidate patients had clinical feature of cytokine storm and certainly need appropriate management. Treatment included non-selective immune suppression with systemic steroid, or selective interleukin-6 inhibition with Tocilizumab and Janus Kinase inhibition with Baricitinib should be considered. Cytokine removal by hemoperfusion could be considered as an alternative treatment of cytokine storm.

Refractory hypoxemia, during VV-ECMO support, could be a life-threatening condition. Optimization of ECMO flow to meet at least 70% of patient's cardiac output should be adjusted, together with maximized post-ECMO membrane blood oxygenation via increasing fractional oxygen and sweep gas flow. Prone position could be considered in a patient who had refractory hypoxemia, did not respond to ECMO support. However, this procedure should be performed by caregiver team with highly experience in prone positioning, to avoid dislocation of all ECMO catheters and other life support devices.

Abnormal coagulation is one of the complications associated with high mortality among COVID-19 patients. Typical feature includes high D-dimer, DIC and multiple vascular occlusions. During ECMO support, close monitoring coagulation function with fine adjust anticoagulant is a crucial management for good outcome. Heparin infusion is still the most commonly used anticoagulant during ECMO support among COVID-19 patients. Activated partial thromboplastin time (APTT) should be monitored every 4-6 hours with target APTT ratio range 1.5-2.0. Enoxaparin is an alternate anticoagulant; however, it needs to be monitored direct factor Xa activity, which may not be available in many situations. Platelet should be maintained above 60,000 particles per mm^3 to prevent internal organs and intracranial bleeding. Another most common bleeding cause in an ECMO support patient is hypofibrinogenemia. It is recommended that cryoprecipitate should be given to keep the fibrinogen level > 100-150 mg/dl in a patient who requires VV-ECMO support for acute respiratory failure from other causes. For COVID-19 patients, the ELSO guideline recommended to keep fibrinogen > 100 mg/dl. However, if there is no clinically significant bleeding, lower fibrinogen level may be tolerated [11].

Recurrent infection, cause by either bacterial or fungal infection, is a common complication among severe COVID-19 patients, especially who received non-selective immunosup-

Table 1. Clinical characters and outcome of severe COVID 19 patients receiving ECMO support

Study	Patients' characters	ECMO outcome	Complications
Early ECMO for Covid-19 experience from China [13]	8 patients Age range 25-81 years BMI 20.8-40.8 kg/sq.m. Pre-ECMO intubation days 4-21 days PaO_2:FiO_2 54-76 cmH_2O	VV-ECMO 88% ECMO support 1-47 days Overall mortality 50%	
Systematic review 13 reported articles from around the world [18]	72 patients Age range 31-81 years BMI range 20.8-41 kg/sq.m.	VV-ECMO 58% Overall mortality 52.8%	Not available
ELSO 2020 213 hospitals 36 countries [14]	1035 patients Age 49 (41-57) years BMI 31 (27-37) kg/sq.m. Pre-ECMO intubation day 4 (2-6) PIP 33 (30-38) cmH_2O PEEP 14 (12-16) cmH_2O PaO_2:FiO_2 72 (59-94) Prone 60% NM blocking agents 72% Steroid 41%	VV-ECMO 96% ECMO support 14 days 90 day mortality 37% Hospital mortality 39%	CNS hemorrhage 6% Tracheostomy 44%
Europe and Israel 177 high experience ECMO centers [15]	Europe and Israel 177 high experience ECMO centers15	VV-ECMO 91% ECMO support 18 days ICU length of stay 33 days Overall mortality 45%	Not available
Paris–Sorbonne University Hospital Network ICUs 3 hospitals in France [17]	83 patients Age 49 (41-56) years BMI 30 (28-34) kg/sq.m. SOFA 12 (9-13) Pre-ECMO intubation day 4 (3-6) IP 18 (16-26) cmH_2O PEEP 14 (12-14) cmH_2O PaO_2:FiO_2 60 (54-68) cmH_2O Prone 94% NM blocking agents 94% Steroid 7%	VV ECMO 98% 35% require ECMO support > 28 days 90 day mortality 36%	Massive bleeding 42% Septic shock 33% Hemorrhagic shock 13% Pulmonary embolism 19%
Middle East and India 19 ECMO centers [16]	307 patients Age 45 (37-52) years BMI 28.6 (25.4-33.3) kg/sq.m. Pre ECMO intubation days 2.5 (1-5) days PaO_2:FiO_2 154 (111-200) cmH_2O	ECMO duration 15 (9.5-24) days Survive ECMO 58% In-hospital mortality 55%	Major bleeding 23.8% Require RRT 31.9% Pneumothorax 7.8%

pression with more than moderate dose of steroid. Frequent sputum surveillant, follow up chest X-ray, blood culture from central lines and blood test for serum galactomannan are recommended for early detection of bacterial and fungal infection. Appropriate antibiotic should be administration for eradicates this infection.

Outcome of ECMO support among COVID-19 patients

The early experience of ECMO support for severe COVID-19 were reported from Republic of China, which enrolled small number of patients, showed that about half of patients died in-hospital [13]. However; recent reports from ELSO registration, using data from 213 hospitals in 36 countries around the world showed that among 1035 patients with COVID-19 who received ECMO support, the median age of patients in ELSO registration was 49 years (IQR 41–57) and median body-mass index was 31 kg/m² (27–37). Most of them (79%) met criteria diagnosis of ARDS and median PaO_2:FiO_2 within 6 h was 72 mmHg (IQR 59–94). VV-ECMO were used in 94% of patients, while 4% of patients received veno-arterial ECMO support. The median duration of ECMO support was 13·9 days (IQR 7·8–23·3) and 44% of patients required tracheostomy. The estimated cumulative incidence of in-hospital mortality 90 days after the initiation of ECMO was 37·4% (95% CI 34·4-40·4). The overall hospital mortality was 39% (380 of 968). The use of ECMO for circulatory support was identified as an independent predictive factor associated with higher in-hospital mortality. Other poor prognostic factors included age > 50 years, on immunosuppressive agents, chronic lung disease, pre-ECMO arrest, acute kidney injury and low PaO_2:FiO_2 ratio [14]. Another report from 177 centers from Europe and Israel enrolled 1531 severe COVID-19 patients receiving ECMO support. The mean age was 52.6 years (range 16–80), 91% receiving VV-ECMO. The mean PaO_2 before ECMO implantation was 65 mmHg. The mean duration of ECMO support at the day of report were 18 days and the mean ICU length of stay was 33 days. At the time of report, 44% of ECMO support died [15]. Recent multicenter international observational from the Middle East and India reported that among 307 COVID-19 patients who received ECMO support, 178 patients (58%) survived after ECMO discontinuation and 138 patients (45%) survived to hospital discharge [16]. Table 1 showed the baseline characters and outcomes among severe COVID 19 patients, requiring ECMO support that was reported in several cohort studies.

Data from a multicenter cohort study that enrolled adult COVID-19 patients from 68 hospitals across the United States showed that in selected patients, ECMO support may reduce mortality among severe respiratory failure patients. At 60 days, 45 of 130 (34.6%) patients who received ECMO died and 553 of 1,167 (47.4%) patients who did not receive ECMO (Hazard ratio 0.55; 95% CI 0.41-0.74) [19]. Although there is no data from a prospective study comparing an outcome of ECMO support for acute respiratory failure due to COVID-19 patients versus acute respiratory failure from other causes, however, data from previous reported data, the in-hospital mortality of severe COVID-19 patients, who require ECMO support, was at least comparable with the severe respiratory failure patients who require ECMO support from other causes [2,3,13-18]. A recent propensity matched analysis showed that ECMO support for COVID-19 patients associated with no different 90-day mortality from non-COVID-19 patients [20].

Conclusion

ECMO support could be considered as a lifesaving procedure for severe COVID 19 patients who did not respond to mechanical ventilator support, despite receiving optimal PEEP titration, neuromuscular blocking agent and prone positioning. The overall hospital mortality was reported about 37-50%, which was comparable with respiratory failure patients, requiring ECMO support from other causes. The decision to initiate ECMO could be depended on the individual hospital capacity and treatment availability.

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ST drafted, submitted and revised manuscript and SK approved the manuscript.

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none

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