

Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019 in Shanghai, China

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Severe cases of coronavirus disease 2019 (COVID-19) cannot be adequately managed with mechanical ventilation alone. The role and outcome of extracorporeal membrane oxygenation (ECMO) in the management of COVID-19 is currently unclear. Eight COVID-19 patients have received ECMO support in Shanghai with seven with venovenous (VV) ECMO support and one veno arterial (VA) ECMO during cardiopulmonary resuscitation. As of March 25, 2020, four patients died (50% mortality), three patients (37.5%) were successfully weaned off ECMO after 22, 40, and 47 days support, respectively, but remain on mechanical ventilation. One patient is still on VV ECMO with mechanical ventilation. The partial pressure of oxygen/fractional of inspired oxygen ratio before ECMO initiation was between 54 and 76, and all were well below 100. The duration of mechanical ventilation before ECMO ranged from 4 to 21 days. Except the one emergent VA ECMO during cardiopulmonary resuscitation, other patients were on ECMO support for between 18 and 47 days. In conclusion, ensuring effective, timely, and safe ECMO support in COVID-19 is key to improving clinical outcomes. Extracorporeal membrane oxygenation support might be an integral part of the critical care provided for COVID-19 patients in centers with advanced ECMO expertise. *ASAIO Journal* 2020; 66:475–481.

Key Words: coronavirus disease 2019, extracorporeal membrane oxygenation, China

Coronavirus disease 2019 (COVID-19) has spread rapidly in China and many other countries since its outbreak due to its person-to-person transmission and its highly contagious nature. The majority of COVID-19 patients suffer mild symptoms and recover completely. However, approximately 14% of cases are severe and 5% are critical with mortality estimates of 2.3%–3.83%.^{1–3} The role of extracorporeal membrane oxygenation (ECMO) in the management of COVID-19 is unclear at this point. It has been used in some patients with COVID-19 in China, but detailed information is unavailable.^{4–7} Extracorporeal membrane oxygenation may have a role in the management of some patients with COVID-19 who have refractory hypoxemic respiratory failure. However, much about the virus is unknown, including the natural history, incidence of late complications, viral persistence, or the prognoses in different subsets of patients.⁸

The World Health Organization (WHO) guidance document includes a statement to consider referring patients with refractory hypoxemia despite lung-protective ventilation in settings with access to expertise in ECMO support.⁹ Similarly, the United States Center for Disease Control provides interim guidance (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>) for clinical management of COVID-19 patients with and without acute respiratory distress syndrome (ARDS).¹⁰ Where ECMO expertise is available, ECMO should be considered according to the standard management algorithm for ARDS in supporting patients with viral lower respiratory tract infection. However, there is little worldwide experience with using ECMO to support COVID-19 patients. A recent Euro Extracorporeal Life-Support Organization adult ECMO-COVID-19 patients survey verified the use of ECMO for COVID-19 in Europe: nine in England, two in German, three in Belgium, 18 in France, 10 in Spain, one in Sweden, one in Poland, one in Czech, and 14 in Italy.¹¹

As of March 22, 2020, 404 COVID-19 cases have been confirmed in Shanghai, China, because the first patient was confirmed on January 20, 2020.⁴ All patients were admitted to a COVID-19-designated hospital, Shanghai Public Health Clinical Center. Extracorporeal membrane oxygenation support has been integrated in the comprehensive COVID-19 management by multidisciplinary teams led by critical care physicians. We aim to share our experiences, core principles, outcomes, and pitfalls in establishing and managing ECMO in critically ill COVID-19 patients and provide guidance on this technique and the resources and expertise required from our initial experience in Shanghai, China.

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Materials and Methods

Shanghai has extensive experience in epidemic prevention and control following the H7N9 crisis in 2013.¹² Since the outbreak of COVID-19 in Wuhan, Hubei Province, in December 2019, Shanghai has closely monitored the progress of COVID-19, registered all available ECMO equipment from local medical centers, and immediately assembled a multidisciplinary COVID-19 ECMO expert team. All confirmed COVID-19 patients were admitted to negative pressure patient units at Shanghai Public Health Clinical Center and managed according to the severity of disease.

To maintain the highest quality of ECMO management, a three member ECMO team with one physician perfusionist, one critical care physician, and one pulmonologist, are available at all times to oversee ECMO management, participate in clinical evaluation and treatment, and communicate with the Shanghai COVID-19 ECMO Expert Team for guidance. A total of 12 ECMO units from Shanghai's major hospitals were enlisted to ensure the needs of critically ill COVID-19 patients, with four units stored outside the hospital as backup. To ensure consistency and standardization among ECMO team members, the ECMO team developed the "Shanghai ECMO Support for COVID-19 Guideline" which was incorporated into the "Shanghai Expert Consensus on Comprehensive Treatment of Coronavirus Disease 2019."¹³

Extracorporeal Membrane Oxygenation Environmental Requirement

All COVID-19 ECMO patients should be placed in a single negative pressure intensive care unit room. Pipeline oxygen and air supply must be available. There should be at least two power outlets dedicated to ECMO and equipped with uninterruptible power supply (UPS), which can support ECMO at full capacity for at least 30 minutes in the case of power failure. Extracorporeal membrane oxygenation equipment should be plugged into the UPS and should not be shared with any other electronic devices. The ECMO water tank and monitors may share a power outlet with other equipment.

Extracorporeal Membrane Oxygenation Equipment and Disposables

The same brand ECMO machine and disposables should be utilized to ensure consistency and safety. The number of ECMO equipment should be maintained at the current number of critically ill COVID-19 patients in the hospital + 2. The number of ECMO kits and cannulas should be maintained at the current number of critically ill COVID-19 patients in the hospital + 4. Activated coagulation time (ACT) cartridges should be calculated based on every 4 hours monitoring per patient and at least 1 week's supply should be available.

Transferred ECMO equipment from other hospitals should be tested for the air and oxygen connections before use. The ECMO centrifugal pump should be examined to ensure that it is able to operate for at least 30 minutes after power loss. The ECMO cart should have a full oxygen cylinder tank with adjustable flow meters (provides continuous oxygen supply for 2 hours at 5 L/minute). Each ECMO unit should have a manual hand crank, four metal pipeline clamps, four plastic pipeline clamps, a tube of ultrasonic coupling agent, a flashlight, and pipeline straps. All ECMO disposables, equipment, and disinfectant kits should

be placed in the ECMO cart and placed within 50 meters of ECMO patients. Disposables should be replaced immediately.

Extracorporeal Membrane Oxygenation Indications and Timing

To avoid organ damage by prolonged hypoxia, standard ARDS treatment should include protective lung ventilation, optimal positive end expiratory pressure, pharmaceutical paralysis, lung recruitment, and prone positioning. If the patient does not improve as indicated by either partial pressure of oxygen (PaO_2)/fractional of inspired oxygen (FiO_2) < 100 mmHg or power of hydrogen (PH) < 7.25 and partial pressure of carbon dioxide > 60 mmHg over 6 hours despite optimal mechanical ventilation, ECMO should be considered. Because some severe COVID-19 patients progress very quickly, ECMO should be immediately established if any of the following criteria are met after failure of aggressive ventilation management and worsening clinical condition: 1) $\text{PaO}_2/\text{FiO}_2 < 50$ mmHg for more than 1 hour. 2) $\text{PaO}_2/\text{FiO}_2 < 80$ mmHg for more than 2 hours, and 3) existence of uncompensated respiratory acidosis with PH < 7.2 for more than 1 hour.

Infection Control in Extracorporeal Membrane Oxygenation Management

During ECMO cannulation, replacement of oxygenators, and other invasive procedures, level 3 infection control precautions should be exercised including the use of Powered Air-Purifying Respirators (PAPR), protective suites, disposable sterile surgical gowns, and three layers of sterile gloves. During routine ECMO rounding, invasive procedures and airway exposure should be avoided. Routine ECMO rounding generally does not require PAPR usage.

Extracorporeal Membrane Oxygenation Establishment

Except for emergency veno arterial (VA) ECMO cannulation during cardiopulmonary resuscitation, all patients should be placed on venovenous (VV) ECMO for the purpose of correcting hypoxia. Before instituting VV ECMO, hemodynamics should be evaluated with point-of-care ultrasound and treated with positive inotropes and vasopressors to maintain hemodynamic stability. The internal jugular vein should be cannulated with a 17Fr arterial cannula, and the femoral vein should be accessed with a 21Fr venous cannula under real-time ultrasound guidance with the Seldinger technique. The tip of the internal jugular vein cannula (Perfusion Cannula; Maquet Cardiopulmonary GmbH, Antalya, Turkey) should be positioned at the junction between right atrium and superior vena cava. The tip of the femoral vein cannula (Drainage Cannula; Maquet Cardiopulmonary GmbH, Antalya, Turkey) should be advanced into the right atrium approximately 1 cm beyond the inferior vena cava junction and avoid cannula tip contacting the interatrial septum using echocardiographic guidance.

The ECMO circuit is prefilled with crystalloid, and the oxygen saturation probe should be routinely placed on the drainage and perfusion cannulas. FiO_2 is initially set to 100%. Extracorporeal membrane oxygenation (Maquet Cardiopulmonary GmbH, Rastatt, Germany) starts from 1 L/minute blood flow and increases 1 L/minute every 30 seconds until the maximum flow is achieved. Peripheral pulse oxygen saturation and mixed venous oxygen saturation are monitored. Cannulas are secured after verification by echocardiography

and surface markers are identified. Then the ECMO flow and sweep rate should be adjusted to maintain peripheral capillary oxygen saturation >90% and mixed venous oxygen saturation >70%. If ECMO flow is inadequate and cannula position seems appropriate per echocardiography imaging, volume should be given (**Figure 1**).

Extracorporeal Membrane Oxygenation Management Goal

The patient's hemoglobin level should be maintained above 11 g/dl throughout the ECMO support. Indices including peripheral arterial oxygenation, ECMO premembrane oxygenation, postmembrane oxygenation, percutaneous oxygenation, and mixed venous oxygenation should be used to determine the patient's oxygen supply and demand balance. Gastrointestinal dysfunction and increased abdominal pressure in COVID-19 patients may directly affect ECMO flow and cause instability.

Extracorporeal Membrane Oxygenation Anticoagulation Management

Extracorporeal membrane oxygenation patients should be anticoagulated using regular heparin followed by a maintenance infusion titrated between 2 and 20 unit/kg/hour to target ACT 180–200 seconds and partial thromboplastin time 50–80 seconds. If heparin resistance is suspected and antithrombin deficiency III activity is low, fresh frozen plasma should be given. In addition, heparin-induced thrombocytopenia (HIT) should be monitored and treated accordingly. When there is significant thrombosis on the ECMO oxygenator, increase in fibrinolysis (D dimer > 10 µg/ml), decrease in fibrinogen (FIB < 1.5 g/L), and thromboelastogram (TEG) signs of hyperfibrinolysis, the ECMO circuit should be replaced. In addition, tranexamic acid should be started (10–20 mg/kg over 3 hours followed by a 1,000 mg, 1–2 mg/kg/hour daily infusion for 2–3 days) and FIB replaced at 1–2 g/days until FIB > 1.5 g/L. If there is significant bleeding or need of invasive procedures, heparin may be reduced or suspended for a maximum period of 24 hours.

Point-of-Care Ultrasound During Extracorporeal Membrane Oxygenation

Point-of-care ultrasound should be performed daily. Ultrasonography of the lungs, heart, abdomen, and vasculature is extremely valuable in this patient population for a multitude of purposes. Lung ultrasound is used to assess indicators of pneumothorax, pleural effusion, lung consolidation, and interstitial changes. Cardiac ultrasound is used to evaluate ejection fraction, pulmonary artery pressure, chamber size, right ventricular/left ventricular function, pericardial effusion, and inferior vena cava diameter. Abdominal ultrasound can help assess bowel peristalsis as well as obstruction, and vascular ultrasound can detect deep venous thrombosis.

Protective Lung Ventilation on Extracorporeal Membrane Oxygenation

The main purpose of mechanical ventilation on ECMO is to protect the lungs and avoid damage to the right heart. An aggressive strategy of protective lung ventilation sets FiO_2 <40%, tidal volume (V_t) 2–4 ml/kg (ideal body weight), plateau pressure <25 cm H_2O , and respiratory rate (RR) 8–10 times/minute. If the plateau pressure exceeds 25 cm H_2O , V_t should be reduced by 1 ml/kg. Pressure control mechanical ventilation is the most commonly used ventilator mode before weaning ECMO. If patient's oxygenation is inadequate, ECMO malfunction should be considered before adjusting ventilator parameters. Sedation and paralysis should be considered in COVID-19 patients with anxiety and high oxygen demand status.

Chest computed tomography (CT) is not routinely performed as transport is considered a patient safety issue. Respiratory mechanics, lung ultrasound, and electrical impedance imaging (electrical impedance tomography [EIT]) are alternative monitoring methods for lung mechanics. Hypercapnia should be initially managed by increasing the VV ECMO sweep rate. During weaning, the RR should be adjusted accordingly, but RR should generally be less than 14.



Figure 1. A coronavirus disease 2019 patient is supported with extracorporeal membrane oxygenation and mechanical ventilation support. [full color online](#)

Awake Extracorporeal Membrane Oxygenation

Coronavirus disease 2019 patients usually develop refractory hyperthermia and other high oxygen consumption states even with effective support. Considering the great difficulty with infection control and unstable pulmonary status in COVID-19 patients, we do not recommend ECMO support without endotracheal intubation.

Continuous Renal Replacement Therapy While on Extracorporeal Membrane Oxygenation

Indications for continuous renal replacement therapy (CRRT) during ECMO are as follows: serum creatinine ≥ 354 $\mu\text{mol/L}$; urine volume <0.3 ml/kg/hour >24 hours; refractory metabolic acidosis with $\text{PH} <7.2$ or $\text{HCO}_3^- <15$ mmol/L; severe electrolyte disturbances including $\text{K} \geq 6.5$ mmol/L; volume overload, such as conjunctival edema, pulmonary edema, congestive heart failure, pleural, and abdominal effusion; sepsis; and multiple organ failure. The above indications could be expanded depending on the severity of COVID-19, and early intervention is advocated. If CRRT equipment is capable of recognizing the ECMO pressure range, the CRRT access line is connected to the port on the ECMO oxygenator, and the CRRT return line is connected to the port between the pump and the oxygenator. Two modes of CRRT are used, continuous venous to venous hemodiafiltration (CVVHDF) and continuous venous to venous hemofiltration (CVVH). To improve dialysis efficiency, CVVH is preferred. If the patient is hypercoagulable or not on anticoagulation, CVVHDF or CVVH combined with CVVHDF could be used. The CRRT dose is usually 28–32 ml/kg/hour for 10–12 hours.

Extracorporeal Membrane Oxygenation Complications

Mouth, nose, and throat bleeding should be controlled by decreasing anticoagulation in addition to ear nose throat consultation. To reduce infections, laboratory testing and blood draws should be minimized. Extracorporeal membrane oxygenation cannulation components need covering with anti-infection transparent dressing with daily inspection and regular disinfection.

Coronavirus disease 2019 patients commonly suffer from flatulence. If abdominal flatulence results in elevated abdominal pressure, the femoral vein drainage can be seriously reduced during ECMO support. If nasal lactulose and enema are ineffective in treatment, traditional Chinese medicine may be considered including nasal administration of 50 ml dachengqi decoction twice a day.

Caution must be taken to avoid ECMO cannula displacement and accidental decannulation. The ECMO circuit should be properly secured to the bedside with avoidance of dropping the equipment to the ground. Bedside nursing staff must be trained to manage ECMO emergencies such as power loss and air/oxygen loss.

Extracorporeal Membrane Oxygenation Weaning Procedures and Standards

Patients with improved chest x-rays, chest CT, arterial blood gas, and respiratory mechanics may attempt ECMO weaning. The sweep to flow ratio is maintained at 1:1, and ECMO flow gradually reduced to 2.5 L/minute while continuing the same

mechanical ventilation parameters. With the ECMO flow maintained at 2.5 L/minute, the ECMO sweep is gradually reduced until there is complete cessation of the sweep. We observe the patient for 6–12 hours after each adjustment. If the patient condition worsens or oxygenation levels are not sustained during the weaning, ECMO parameters are restored to previous settings. To take patients off ECMO, the following criteria must be maintained for 24–48 hours at ECMO flow rates of 2.5 L/minute without sweep: hemodynamic stability; improvements in chest x-ray, chest CT, EIT, or lung ultrasonography; $\text{PaO}_2/\text{FiO}_2 >150$ mmHg, $\text{PCO}_2 \leq 50$ mmHg, and $\text{RR} \leq 20$; body temperature $<38^\circ\text{C}$; Murray index: 2–3; hematocrit $>35\%$ (**Figure 2**).

Results

Extracorporeal membrane oxygenation was necessary for 8 out of the 16 critically ill COVID-19 patients in whom severe hypoxia could not be reversed with optimized mechanical ventilation.

On January 30, 2020, the first VV ECMO for a COVID-19 patient with severe hypoxia that could not be reversed by aggressive mechanical ventilation was established. To date, eight COVID-19 patients have received ECMO: seven with VV ECMO support and one patient was emergently placed on VA ECMO during cardiopulmonary resuscitation. As of March 25, 2020, four patients died (50% mortality). Three patients were successfully (37.5%) weaned off ECMO after 22, 40, and 47 days support, respectively, but remain on mechanical ventilation. One patient is still on VV ECMO with mechanical ventilation. Patient 7 received ECMO initially on January 30, 2020, for 8 days and weaned off. His condition deteriorated on February 12, 2020, and ECMO had to be restarted again. He died after 10 days of ECMO support the second time.

Two patients were female, and six were male. The age range was from 25 to 81 years old. Four patients had hypertension, and two patients had cerebral infarct medical history. The $\text{PaO}_2/\text{FiO}_2$ ratio before ECMO initiation were between 54 and 76, and all were well below 100. The duration of mechanical ventilation before ECMO ranged from 4 to 21 days. Except the one emergent VA ECMO during cardiopulmonary resuscitation, other patients were on ECMO support for between 18 and 47 days (**Table 1**).

Discussion

Extracorporeal membrane oxygenation has been used clinically in Shanghai for nearly 19 years. Cross-training, academic exchange, as well mutual support among perfusionists, critical care physicians, pulmonologists, cardiologists, and emergency medicine physicians have created a solid foundation for the successful implementation of ECMO programs in this area during crises. Extracorporeal membrane oxygenation support in the prevention and control of the highly pathogenic avian influenza H7N8 in 2013 provided our team valuable experience. The Shanghai ECMO Clinical Quality Control Registry in 2018 properly prepared ECMO-capable hospitals and departments for the timely enlisting of equipment and ECMO experts during the COVID-19 crisis.¹⁴

Diffuse pulmonary edema and hyaline membrane formation are the main pathologic features in COVID-19 patients.¹⁵ Hypoxia can progress rapidly, and optimal mechanical ventilation

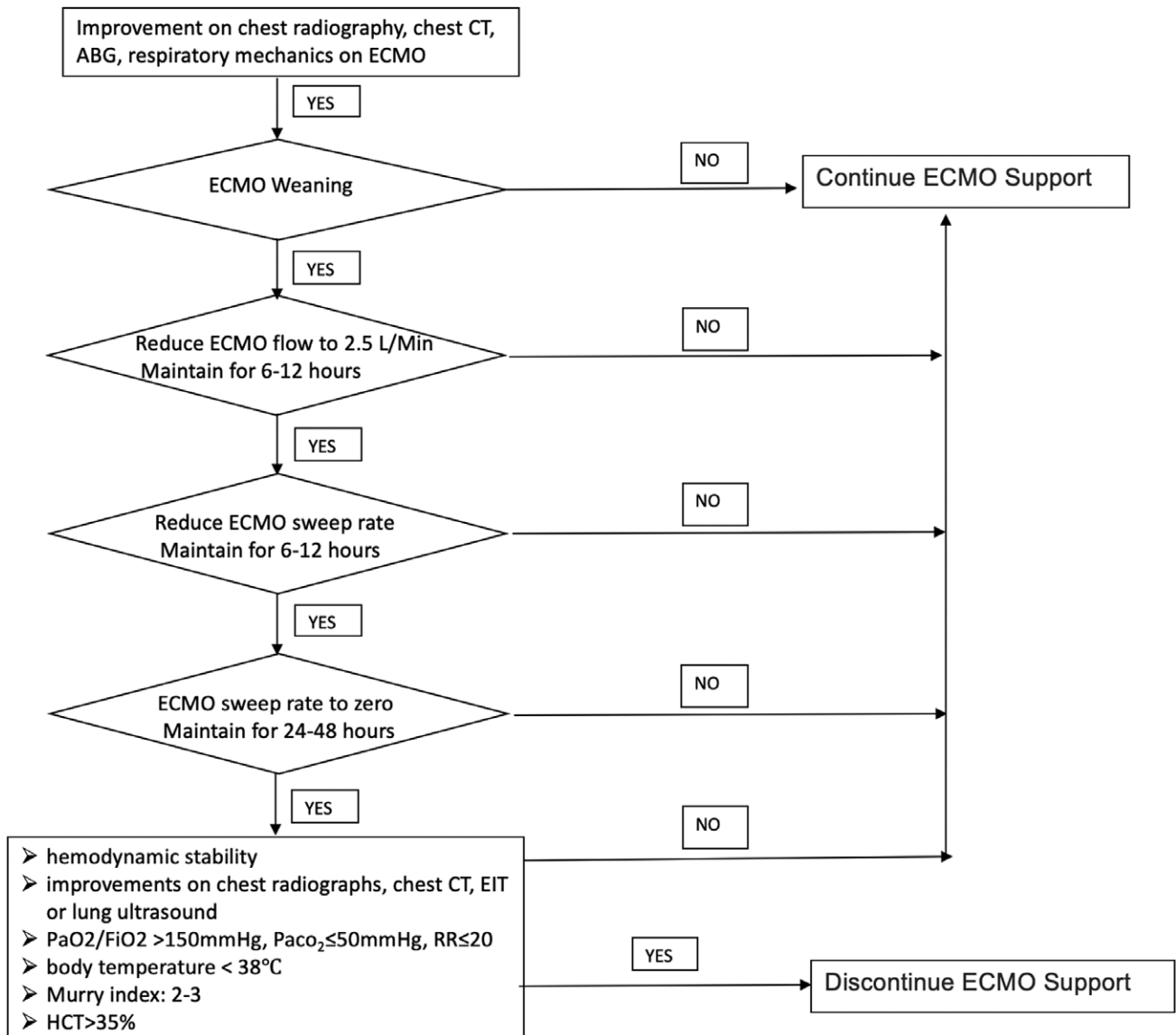


Figure 2. Flowchart of ECMO weaning protocol in COVID-19 patients. ABG, arterial blood gas; COVID-19, coronavirus disease 2019; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; EIT, electrical impedance tomography; FiO₂, fractional of inspired oxygen; HCT, hematocrit; PaCO₂, partial pressure of carbon dioxide; PaO₂, partial pressure of oxygen; RR, respiratory rate.

might not be enough to correct for patients in critical status. Traditional ECMO indications, or the standards as adopted in the extracorporeal membrane oxygenation for severe acute respiratory distress syndrome study,¹⁶ may lead to prolonged hypoxia and multiple organ failure in these patients. Therefore, we recommend early establishment of ECMO when mechanical ventilation is insufficient to correct hypoxia in COVID-19 patients. Our indications are consistent with the latest version of the COVID-19 Diagnosis and Treatment Guidelines (Version 7).¹⁷

The safety and success of ECMO in the Shanghai Public Health Clinical Center were challenged by many factors including, but not limited to, strict infection control requirements, unfamiliar team members in new environments, and slow communication and feedback in isolation wards. Lessons learned from prior crisis experiences including equipment check before use, management of gas and electrical emergency hazards,

availability and location of ECMO disposables, and proactive alarm management to avoid disturbances to unfamiliar health-care providers were invaluable for our team and the hospital.

It is understood that ECMO does not provide direct support for organs other than the lungs or heart beyond increasing systemic oxygen delivery and mitigating ventilator-induced lung injury. A substantial proportion of critically ill patients with COVID-19 appear to have developed cardiac arrhythmias or shock, but it is unknown how many have or will develop refractory multiorgan failure, for which ECMO may be of more limited use.⁸ More data on the mechanism of death and disease are required to determine whether ECMO is appropriate to offer to COVID-19 patients. However, it appears that the damage and duration of lung injuries in COVID-19 are extensive, and prolonged ECMO support might be required as shown in our study.

Table 1. COVID-19 Patients' Data Who Had Received ECMO Support as of March 25, 2020 in Shanghai, China

Patient	1	2	3	4	5	6	7	8
Clinical characteristics								
Date of admission	2 February	28 January	30 January	1 February	1 February	22 January	29 January	9 February
Gender	Male	Male	Male	Male	Male	Female	Male	Female
Age (years)	64	81	62	75	65	63	25	79
Weight/BMI (kg)	76/24.5	72/23.8	75/24.3	67/22.4	62/20.8	65/24.2	125/40.8	74/23.6
Date of mechanical ventilation	9 February	28 January	6 February	1 February	14 February	31 January	30 January	13 February
Comorbidities								
Hypertension	Yes	Yes			Yes			Yes
Diabetes					Yes			
Cardiovascular disease		Yes						
Malignancy				BC				
Cerebrovascular disease					CI			CI
COPD								
Chronic kidney disease					MN			
Murray Score	4	4	4	4	4	4	4	4
ECMO parameters								
RASS	-3 to -5	-3 to -5	-3 to -5	-3 to -5	-3 to -5	-3 to -5	-3 to -5	NA
P/F before ECMO	67	66	64	75	76	70	54	57
Lactate (mmol/L)	2.4	2.8	3.1	4.0	1.3	2.4	3.1	2.1
Duration of mechanical ventilation before ECMO	4	10	12	13	4	21	5* 13*	5
Date of ECMO initiation	13 February	7 February	6 February	14 February	18 February	21 February	30 January* 12 February*	18 February
Perfusion Cannula	IJV-17Fr	IJV-17Fr	IJV-17Fr	IJV-17Fr	IJV-17Fr	IJV-17Fr	IJV-17Fr* IJV-17Fr*	FA-17
Drainage Cannula	FV-21Fr	FV-21Fr	FV-21Fr	FV-21Fr	FV-21Fr	FV-21Fr	FV-23Fr* FV-23Fr*	FV-21
Time on ECMO (days)	40	47	47	37	22	33	8/10	3 hours
Mode of ECMO	VV	VV	VV	VV	VV	VV	VV	ECPR-VA
Current state	Recovery	Died	Recovery	Died	Recovery	On ECMO	Died	Died

*Patients 7 received ECMO initially on January 30, 2020, for 8 days and weaned off. His condition deteriorated on February 12, 2020, and ECMO had to be restarted again.

BC, bladder cancer; BMI, body mass index; CI, cerebral infarction; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; ECPR-VA, extracorporeal cardiopulmonary resuscitation-veno-arterial; FA, femoral artery; FV, femoral vein; IJV, internal jugular vein; MN, membranous nephropathy; NA, not available; P/F, partial pressure of oxygen (PaO₂) divided by fractional of inspired oxygen (FiO₂); RASS, Richmond Agitation-Sedation Score; VV, venovenous.

Extracorporeal membrane oxygenation is highly resource consumptive, and many COVID-19 affected countries might not be able to afford this expensive technology. In less well-resourced countries, many more lives will be saved by ensuring that oxygen and pulse oximetry are widely available. Confirmation of the diagnosis, appropriate quarantine and oxygen therapy alone might save many lives with minimal cost. Mechanical ventilation or, for those most likely to benefit, ECMO needs to be evaluated for benefits/risks on a case-by-case basis.⁸

In conclusion, ensuring effective, timely, and safe ECMO support in COVID-19 is key to improving clinical outcomes. Extracorporeal membrane oxygenation support might be an integral part of the critical care provided for COVID-19 patients in centers with advanced ECMO expertise.

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