Turkish Society of Cardiovascular Surgery (TSCVS) Proposal for use of ECMO in respiratory and circulatory failure in COVID-19 pandemic era

COVID-19 pandemi çağında solunum ve dolaşım yetmezliğinde ECMO kullanımına ilişkin Türk Kalp ve Damar Cerrahisi Derneği (TKDCD) önerileri

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ABSTRACT

The document is prepared to guide the members of the The Turkish Society of Cardiovascular Surgery (TSCVS) and other extracorporeal membrane oxygenation (ECMO) centers worldwide to share experiences in using ECMO in COVID-19 pandemic.

Keywords: Extracorporeal membrane oxygenation, pandemics, respiratory distress syndrome, shock.

ÖZ

Bu doküman Türk Kalp ve Damar Cerrahisi Derneği (TKDCD) dernek üyelerine ve tüm dünyadaki diğer ekstrakorporeal membran oksijenasyon (ECMO) merkezlerine rehberlik etmesi ve COVID-19 pandemisinde ECMO kullanımına ilişkin deneyimleri paylaşmak amacıyla hazırlanmıştır.

Anahtar sözcükler: Ekstrakorporeal membran oksijenasyonu, pandemi, solunum zorluğu sendromu, şok.

THE MAJOR CLINICAL PROBLEM

Coronavirus disease 2019 (COVID-19) is an explosive viral pandemic of zoonotic origin. The disease is threatening the entire world and is potentially fatal.[1] Using the electron microscopic images, description of the structure, and genomic features of the new virus, it was named as novel severe acute respiratory syndrome (SARS)-CoV-2. Novel SARS-CoV-2 virus is highly transmissible through person-to-person contact with respiratory droplets. It is well defined that an essential feature of a new virus is the capacitance of being highly infectious (R0: 2.2).[2,3] Transmission may occur from both symptomatic and asymptomatic patients.[4] Viral human cell invasion is maintained by the angiotensin-converting enzyme-2 (ACE-2) receptor.Among hospitalized cases, the severe disease was reported in 15% of the cases, and fatality occurred in 12% of these cases, with higher case-fatality rates in older adults.[5]

The Chinese health authorities reported the first cluster of cases (n=41) with COVID-19 to the World Health Organization (WHO) on the date of December 31, 2019. Epidemiological studies have suggested the exposure to Huanan Seafood Wholesale Market in this cluster, and the market was closed on January 1, 2020. Phylogenetic analysis of the complete viral genome of the single patient who was a worker at the market revealed that the virus was most closely related

(89.1% nucleotide similarity) to a group of SARS-like coronaviruses.[6] Later on, it was shown that the new type of coronavirus originated in bats and was transmitted to humans through unknown intermediary animals in Wuhan, Hubei province of China.[7] As a result of global spread, the outbreak has been labeled as a pandemic by the WHO on March 11, 2020.

As of March 25, 416,916 cases were reported in Europe with a rate of 30% hospitalization and 4% severe illness.[5] In Turkey, as of March 26, the number of patients has been exponentially growing and, currently, it exceeds 2,433 with 59 fatalities. The first case was reported on March 11, 2020 by the Turkish Ministry of Health and first death due to COVID-19 on March 16, 2020.

Clinical characteristics of coronavirus disease 2019 in China showed that the median age was 47 years and 41.9% of the patients were females.[8] The presentation of COVID-19 was typical with symptoms of fever, dry cough, fatigue, and shortness of breath.[9] However, it can be also clinically asymptomatic. The virus may cause severe respiratory failure by the massive alveolar damage involving the lower respiratory tract or severe acute respiratory distress syndrome (ARDS). COVID-19 can be fatal, particularly in elderly patients and those with comorbidities. Postmortem biopsies showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates, interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, desquamation of pneumocytes, and hyaline membrane formation.[10] The pathological features of COVID-19 much resemble those seen in SARS and Middle East respiratory syndrome (MERS) coronavirus infection.

According to Chinese experience, older age was associated with a higher risk of development of ARDS and death likely due to impaired immune responses.[11] Another multi-center study showed that older age (odds ratio 1.10, 95% CI: 1.03-1.17, annual increase; p=0.0043), higher Sequential Organ Failure Assessment (SOFA) scores (5.65, 2.61-12.23; p<0.0001), and D-dimer higher than 1 mug/L (18.42, 2.64-128.55; p=0.0033) on admission were associated with a poor prognosis.[12]

The rate of ARDS ranges from 15 to 30% among patients who require hospitalization.[13] In case of severe ARDS, adequate tissue oxygenation cannot be optimized, despite maximal mechanical ventilatory support and other treatment strategies. In addition, COVID-19 can cause myocardial injury in approximately 7% of patients leading to myocardial dysfunction.[14] Cardiovascular comorbidities pose an independent risk for mortality.[12]

In the most recent study, Shi et al.[15] demonstrated that cardiac injury, as a common complication (19.7%), was associated with significant mortality rates. The authors showed that patients with cardiac injury presented with more severe acute illness as manifested by abnormal laboratory results such as higher levels of C-reactive protein, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and creatinine levels accompanied by more aggressive computed tomography (CT) findings such as multiple mottling and ground-glass opacities. These patients had severe ARDS, and a higher proportion of them required non-invasive or invasive ventilation.[15] Similarly, of these patients with documented cardiac injury, 58% and 60% had a history of hypertension, while 25% and 30% had a previous cardiac disease in Wang and Shi's reports, respectively.[15,16] Both in cases of respiratory and circulatory failure, refractory to the treatments, extracorporeal life support (ECLS) may be needed.

COVID-19 and ARDS

Following the incubation period of 2 to 14 days, symptoms may occur, patients are admitted to hospital in approximately 7 days (range, 4 to 8 days), develop shortness of breath, appears in approximately 8 days (range, 5 to 13 days), and need mechanical ventilation support within 10.5 days (range, 7 to 14 days).[17] Expert anesthesiologists from China have recently reported recommendations for tracheal intubation in critically ill patients with COVID-19.[18]

Chest imaging findings in patients with COVID-19 are of utmost importance for an objective evaluation of the lung lesions.[19-21] Thin-section CT is not specific for the final diagnosis, but sensitive for the detection, despite negative real time-polymerase chain reaction (RT-PCR) results. Ground glass opacities, consolidation, reticular pattern, and crazy paving pattern are typical CT manifestations of COVID-19.[22,23] In the presence of bilateral, peripheral, posterior or lower zone infiltration, COVID-19 should be suspected.[23,24] The most significant feature of pneumonia caused by SARS-CoV-2 is rapid progression to ARDS, which is seen in 32% of cases.[25]

In general, ARDS can be classified as mild, if the partial pressure of oxygen in arterial blood (PaO_2)/ fraction of inspired oxygen (FiO_2) value is between 200 and 300 mmHg; moderate, if the PaO_2/FiO_2 value is between 100 and 200 mmHg; and severe, if the PaO_2/FiO_2 value is below 100 mmHg, while the positive end-expiratory pressure (PEEP) is below

5 cmH$_2$O. Patients who develop ARDS should be treated according to treatment protocols launched by national and international organizations including high flow oxygen therapy, non-invasive mechanical ventilation for eligible patients, mechanical ventilation, and prone position, if needed.

COVID-19 and MYOCARDIAL INJURY

The most challenging clinical scenarios of COVID-19 are respiratory failure, secondary bacterial infections, septic shock, and multiorgan failure induced by ARDS. In addition, myocardial injury and associated complications, such as low cardiac output and arrhythmia, may present with COVID-19.[16] Although cardiac enzymes can be affected during different types of respiratory diseases, myocardial injury due to COVID-19 is caused by several other factors. This condition, called non-coronary (Type II) myocardial infarction, is associated with hypoxia, excessive inflammatory response, and direct damage of the SARS-CoV-2 toward cardiomyocytes.[26]

The use of right heart catheterization to differentiate whether a pulmonary disease causes the right heart failure is taken out from the Berlin Criteria for the patients with ARDS. In these patients, troponin and BNP levels and echocardiographic evaluation can help to make the differential diagnosis. While discussing the indication of extracorporeal membrane oxygenation (ECMO), differentiating whether the cardiogenic shock is developed or not, plays an essential role in the decision of which type of ECMO should be applied: veno-arterial (VA) or veno-venous (VV) and appropriate site of cannulation. However, the prognosis cannot be improved in patients with severe ARDS due to COVID-19, even with the support of ECMO. In addition to this, there is no case reported for the use of ECMO for fulminant myocarditis caused by COVID-19 in the literature. Therefore, there is no consensus and sufficient evidence for the indication, implantation, and weaning of ECMO in these patients.

COVID-19 and CARDIOVASCULAR DISEASES

COVID-19 pandemic puts a great responsibility on cardiologists and cardiovascular surgeons on differentiating elective, urgent, and emergency cases to be performed. In certain countries as in Turkey, intensive care unit beds are still available, but may not be available in the coming days. The ethical dilemma is expected to be solved soon with international collaboration.

WORLDWIDE OUTCOMES OF ECMO SUPPORT in COVID-19 PANDEMIC

Although the number of cases is exponentially increasing all over the world day by day, the number of patients undergoing ECMO is quite limited.[12,16,27-29] The most important reason for this may be that they have not been published yet. The results obtained from the series published in a short time are shown in Table 1.

RISK ASSESSMENT FOR MORTALITY in COVID-19 PANDEMIC

COVID-19 infection can create severe clinical pictures with pneumonia, ARDS, shock, and multiorgan failure. In particular, due to the limited number of ECMO devices and excessive workload of the healthcare professionals, it is vital to select the right patients who will benefit maximum. Therefore, it is necessary to know the risk factors for mortality in COVID-19. According to the available evidence within a relatively short period, the most critical risk factors for mortality are:

a. Patient characteristics and comorbidities at the time of hospital admission[12,16,30] advanced age, hypertension, coronary artery disease [CAD],

Table 1. The data and outcomes of ECMO support for COVID-19 patients up to date

	Patients Hospitalized	Patients requiring ICU		Patients requiring ECMO	Wean	On ECMO	Successful weaning from ECMO	Mortality	
	n	n	%	n	n	n	n	n	%
Wang et al., 2020[16]	138	36	26	4	NA	NA	NA	NA	
Huang et al., 2020[27]	41	13	32	2	NA	NA	NA	NA	
Chen et al., 2020[28]	99	23	23	3	NA	NA	NA	1	33
Yang et al., 2020[29]	710	52	7	6	None	1	None	5	83
Zhou et al., 2020[12]	191	50	26	3	None	None	None	3	100

ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; NA: Not applicable

diabetes mellitus [DM], chronic obstructive pulmonary disease [COPD], chronic renal failure, history of malignancy, high SOFA scores

b. Laboratory findings obtained at the time of hospital admission[12,16,27] leukocytosis, lymphopenia, anemia, thrombocytopenia, high alanine aminotransferase, high lactate dehydrogenase, high creatine kinase, high troponin, high D-dimer, prolonged prothrombin time, high ferritin, high IL-6, high procalcitonin.

ECMO EXPERIENCE DURING PREVIOUS PANDEMICS

In 2009, during a Swine Flu pandemic, the Extracorporeal Life Support Organization (ELSO) data from Australia and New Zealand were published. Sixty-eight patients received ECMO support for ARDS. The median duration of support was 10 (range, 7 to 15) days, and the ICU and hospital discharge rate was 71% and 47% at the time of publication.[31]

During the MERS outbreak originating from another type of coronavirus in 2014, a comparative analysis of 17 patients who received ECMO support and 18 patients in the conventional treatment group showed a lower mortality rate in the ECMO group (65% vs. 100%, respectively).[32]

CONSIDERATION OF ECMO SUPPORT IN COVID-19

In case of persistent hypoxia and hypercarbia despite all the treatment strategies recommended by the national and international guidelines for the adult patient with COVID-19, ECMO support can be considered in patients who meet the following pulmonary criteria:

Patients with respiratory insufficiency who are under mechanical ventilatory support for less than 7 days and

a. PEEP >12-16 cm H_2O

b. The tidal volume of 4-6 mL/kg

c. Plateau pressure >30 cmH_2O

d. FiO_2 >80%

e. PaO_2/FiO_2 between 100-150 mmHg

f. $PaCO_2$ >60 mmHg (for more than 6 h)

g. Blood pH <7.25 (arterial blood gas analysis)

h. Respiratory rate >35 breaths per min (for 7 min)

i. Refractory to prone positioning

In case of persistent cardiogenic shock, refractory to all positive inotropic and vasopressor agents and intra-aortic balloon pump, ECMO therapy can be considered in patients who meet the following cardiac criteria:

a. Left ventricle ejection fraction below %30 without a history of cardiac disease

b. Progressive deterioration of systolic function; or right heart failure/low cardiac output with accompanying high pulmonary artery pressure.

RECOMMENDATIONS (Figure 1)

INDICATIONS FOR ECMO SUPPORT

1. Patients with COVID-19 without any comorbidity

2. Rapidly progressive pneumonia

3. Severe ARDS

4. Diffuse lung injury by SARS-CoV-2 as confirmed by CT scan

5. Patients under the age of 65 years

6. High probability for recovery of pulmonary functions

CONTRAINDICATIONS FOR ECMO SUPPORT

1. Elderly patients

2. Any age with severe comorbidities (CAD, COPD, DM with end-organ damage, chronic renal failure, end-stage liver failure, known systemic disease, permanent neurological damage, malignancy)

3. Bacterial superinfection

4. Sepsis

5. Disseminated intravascular coagulation

6. Septic shock

Patients who are suitable for these criteria should be considered for ECMO by the Team consisting of the experts from Cardiovascular Surgery, Anesthesiology and Intensive Care, Infectious Diseases, Cardiology, and Respiratory Medicine.

RECOMMENDATIONS FOR ECMO APPLICATIONS

1. VV-ECMO with routine VV cannulation should be considered in the first place, when ECMO decision is made due to ARDS with aforementioned clinical respiratory status,
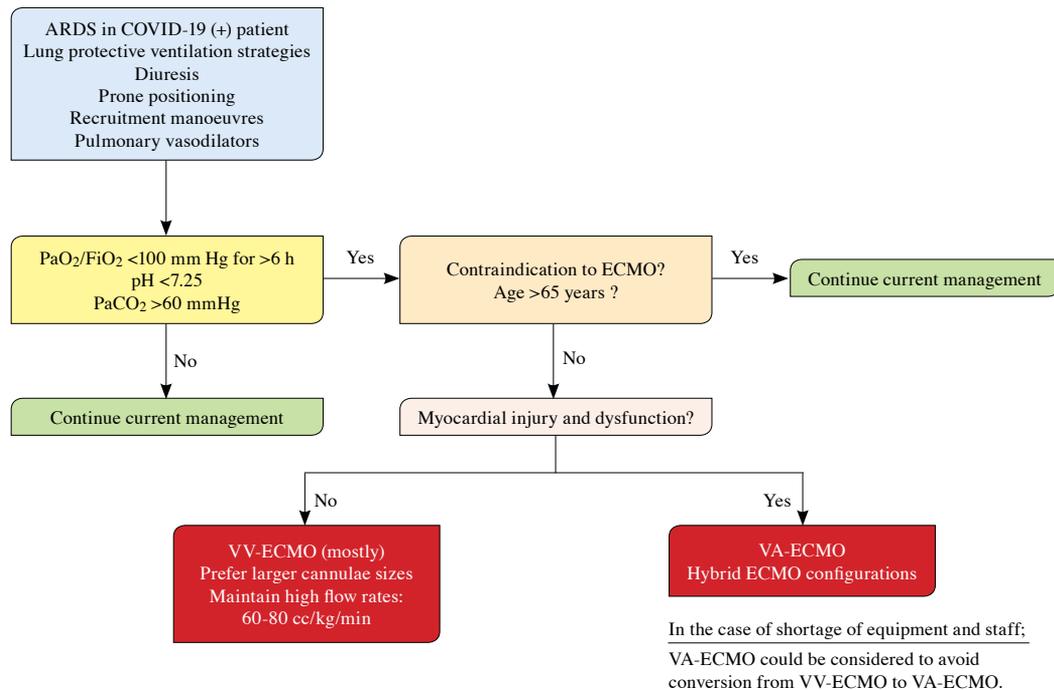
Figure 1. Recommended algorithm for the management of ECMO use in COVID-19.

ARDS: Acute respiratory distress syndrome; ECMO: Extracorporeal membrane oxygenation; VV: Veno-venous; VA: Veno-arterial.

2. In patients with myocardial dysfunction by echocardiographic evaluation, VA-ECMO should be considered.

3. In patients without myocardial dysfunction, VA-ECMO can be considered in the following situations:

   a) Patients older than 45 years without any known cardiac or systemic comorbidities, but the history of smoking or antihypertensive medication or other risk factors for CAD, that may be prone to myocardial dysfunction during support

   b) New myocardial dysfunction during VV-ECMO

   c) In selected cases, to decrease the need for conversion from VV-ECMO to VA-ECMO, if the shortage of equipment and staff is concerned

4. The axillary/subclavian route is suggested for the VA-ECMO to prevent cerebral and coronary hypoxia. For venous cannulation, jugular and femoral routes are optional. If oxygenation is insufficient during the VA-ECMO run, connecting an additional venous inflow for Veno-Arterial-Venous (VAV)-ECMO can be considered.

5. Femoral cannulation should be avoided. If performed thoroughly, a jugular venous cannula should be routinely used to run as VAV-ECMO. The use of an intra-aortic balloon pump (IABP) can be considered in case of insufficient hemodynamic recovery.

6. If the arterial cannula is placed into the femoral artery, distal perfusion cannula should be placed.

7. Oxygenation should always be followed by the PaO_2 levels from the arterial blood gas obtained from the right radial artery.

8. Cardiac functions should be monitored regularly during VV-ECMO.

9. Additional procedure (i.e., venting cannula or IABP) for left ventricular unloading should be considered in case VA-ECMO.

10. All the health careers should be supplied with maximal personal protection equipment during the procedure.

11. The number of health careers during the procedure should be kept minimal.

12. Anticoagulant therapy should be applied regularly, unless bleeding or coagulopathy occurs.

13. Functions of the ECMO device and the data of hemodynamics should be recorded daily by the perfusionists.

14. *Despite all the difficulties in a pandemic workload, ECMO decision should be still made by the ECMO Team, and its application should be kept very limited due to unpromising results.*

In conclusion, the global outbreak of COVID-19 has again reminded us of the Hippocratic Oath and Principles. Early written recommendations during this pandemic may help healthcare professionals who are under high physical, emotional, and spiritual stress. The indications and contraindications for the levels of cardiopulmonary support in patients with COVID-19 require close international collaboration and sharing the outcomes in transparency.

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