Extracorporeal membrane oxygenation in the management of critically ill patients with coronavirus disease 2019: A narrative review

ALEXANDRU FLORIN PLEȘOIANU[1*], CARMEN ELENA PLEȘOIANU[2,3*], IRIS BARARU-BOJAN (BARARU)[4], MARIA-CRISTINA VLĂDEANU (APĂVĂLOAEI)[4], ANDREI BOJAN[1], ANDREI ȚĂRUȘ[5,6] and GRIGORE TINICĂ[5,6*]

[1]Department of Surgical Science, 'Grigore T. Popa' University of Medicine and Pharmacy; [2]Department of Internal Medicine, Faculty of Medicine, 'Grigore T. Popa' University of Medicine and Pharmacy, Iași 700115; [3]Department of Clinical Cardiology, 'Prof. Dr. George I.M. Georgescu' Institute of Cardiovascular Diseases, Iași 700503; [4]Department of Pathophysiology, Morpho-Functional Sciences, Faculty of Medicine, 'Grigore T. Popa' University of Medicine and Pharmacy; [5]Department of Cardiovascular Surgery, Faculty of Medicine, 'Grigore T. Popa' University of Medicine and Pharmacy, Iași 700115; [6]Department of Cardiovascular Surgery, 'Prof. Dr. George I.M. Georgescu' Institute of Cardiovascular Diseases, Iași 700503, Romania

Received July 2, 2021; Accepted August 3, 2021

DOI: 10.3892/etm.2021.10731

Abstract. What started with 41 hospitalized patients identified as having laboratory-confirmed coronavirus disease 2019 (COVID-19) in Wuhan, China, by January 2, 2020, turned into an unprecedented pandemic with more than 113 million confirmed cases and a mortality exceeding 2.5 million deaths worldwide by the beginning of March 2021. Although the course of the disease is uneventful in most cases, there is a percentage of patients who become critically ill and need admission in the intensive care unit for severe respiratory failure. Numerous of these patients undergo invasive mechanical ventilation and have an extremely high mortality rate. For these patients, extracorporeal membrane oxygenation (ECMO) has emerged as a last standing resource. In the present study, the literature was reviewed to evaluate the worldwide data regarding the use of ECMO in the management of critically ill COVID-19 patients. ISI Thomson Web of Science was searched for articles with English language abstracts from inception to March 1, 2021, with 'ECMO in COVID-19' as key words. A total of 214 abstracts were screened (case reports, guidelines, reviews) and the most relevant articles were included in the present review. The use of ECMO in the management of critically ill patients with COVID-19-induced acute respiratory distress syndrome refractory to conventional mechanical invasive ventilation is increasing. By increasing the survival rate from less than 20% to more than 50%, ECMO proved to be a valuable resource in the management of the most challenging critically ill COVID-19 patients.

Correspondence to: Dr Carmen Elena Pleșoianu, Department of Internal Medicine, Faculty of Medicine, 'Grigore T. Popa' University of Medicine and Pharmacy, 16 Unirii Street, Iași 700115, Romania
E-mail: carmenplesoianu@gmail.com

Dr Andrei Țăruș, Department of Cardiovascular Surgery, 'Prof. Dr. George I.M. Georgescu' Institute of Cardiovascular Diseases, 50 Carol I Boulevard, Iași 700503, Romania
E-mail: andrewtarus@gmail.com

*Contributed equally

Key words: extracorporeal membrane oxygenation, coronavirus disease 2019, SARS-CoV-2, pandemic, mechanical support, acute respiratory failure, critically ill patients

Contents

1. Introduction

What started with 41 hospital admitted patients identified as having laboratory-confirmed coronavirus disease 2019 (COVID-19) in Wuhan, China by January 2, 2020 (1) turned into an unprecedented pandemic declared by the World Health Organization (WHO) on March 11, 2020 (2) that reached 113,820,168 confirmed cases, including 2,527,891 deaths by the beginning of March 2021 (3). The severity of SARS-CoV-2 infection ranges from an asymptomatic carrier state to severe hypoxemic respiratory failure (4). While in most cases the course of the disease is uneventful, there is a percentage of patients who develop a severe disease with critical hypoxia in relation with pneumonia and require admission in the intensive care unit (ICU) for advanced treatment and even invasive mechanical ventilation (IMV) (5,6). For the patients who have an increased mortality rate (7) on conventional management, extracorporeal membrane oxygenation (ECMO) has emerged as a last standing resource (8).

In the present review, the literature was analyzed to evaluate the worldwide data regarding the use of ECMO in the management of critically ill COVID-19 patients. ISI Thomson Web of Science was searched for 'ECMO in COVID-19' from inception to March 1, 2021. A total of 214 abstracts were screened (case reports, guidelines, reviews) and the most relevant articles were included in this review.

2. Worldwide data regarding the critically ill COVID-19 patients

There are substantial differences between countries and regions regarding data on critically ill COVID-19 patients.

Guan *et al* reported data from 1,099 patients with laboratory-confirmed COVID-19 between December 11, 2019 and January 29, 2020, from 552 hospitals in China (median age 47 years, 58.1% male). From the 173 (15.7%) patients reported to have a severe disease (median age 52 years, 57.8% male), 33 (19.1%) patients were admitted to the ICU, 25 (14.5%) underwent IMV and 5 (2.9%) patients received ECMO (9). At the cutoff data for the study (January 31, 2020), 89% of the patients with severe disease were still hospitalized, 2.9% had been discharged from hospital, 1.2% recovered and 8.1% had succumbed (9). Similar data regarding the overall rate of severe cases (16.0%) was reported by Liang *et al* (10).

Grasselli *et al* reported data from 1,591 critically ill patients with laboratory-confirmed COVID-19, between February 20, 2020 and March 18, 2020, admitted to ICUs in 72 hospitals in the Lombardy region of Italy (median age 63 years, 82% male) (11). Out of 1,300 patients with available respiratory support data, 1,150 (88%) patients required IMV (11). After seven days of follow-up, among the 1,581 patients with ICU available data, 256 (16%) had been discharged, 920 (58%) were still in the ICU, and 405 (26%) had succumbed (11).

Docherty *et al* reported data from 20,133 hospitalized patients with COVID-19 between February 6, 2020 and April 19, 2020, from 208 hospitals in England, Wales and Scotland (median age 73 years, 60% male) (12). At 2 weeks follow-up, out of the 3,001 (17%) patients admitted to the ICU, 41% (1,217/3,001) continued to receive care, 28% (826/3,001) were discharged alive, and 32% (958/3,001) had succumbed (12). Out of the 1,658 patients who underwent IMV, 46% (764/1,658) remained in the hospital, 17% (276/1,658) were discharged alive, and 37% (618/1,658) had succumbed (12).

Richardson *et al* reported data from 5,700 patients with laboratory-confirmed COVID-19 hospitalized in the New York City area between March 1, 2020 and April 4, 2020 (median age 63 years, 60.3% male) (13). At the cutoff data for the study (April 4, 2020), among patients who were discharged or had succumbed (n=2,634), 373 (14.2%) patients were treated in the ICU (median age 68 years, 66.5% male), 320 (12.2% of the total population and 85.8% of the patients admitted to the ICU) received IMV, and 553 (21%) had succumbed (13). A total of 282 out of 320 patients (88.1%) who underwent IMV had succumbed compared with 271 out of 2,314 (11.7%) for those who did not require this strategy (13). At the cut off data for the study, for patients requiring IMV (n=1,151, 20.2%), 831 (72.2%) remained in the hospital, 38 (3.3%) were discharged alive, and 282 (24.5%) had succumbed (mortality rates for 18-65 and older-than-65 age groups were 76.4 and 97.2%, respectively for the mechanically ventilated patients compared with the patients of the same age intervals but not receiving mechanical ventilation that were 1.98 and 26.6%, respectively) (13).

Peckham *et al* revealed in a meta-analysis of 3,111,714 reported global cases that, while there is no difference in the proportion of males and females with confirmed COVID-19, male patients have almost three times the odds of requiring ICU admission and higher odds of death compared with females (14).

3. Rational for ECMO use in the management of critically ill COVID-19 patients

ECMO is a method of extracorporeal circulation and ventilation support, primarily adopted to partially or completely replace the cardiopulmonary function of patients to protect the oxygen supply of the organs and strive for time to treat primary diseases (15). It is a form of modified cardiopulmonary bypass in which venous blood is removed from the body and pumped back through an artificial membrane lung in patients who have refractory respiratory or cardiac failure (4). The primary indication for ECMO is acute severe heart or lung failure with high mortality risk despite optimal conventional therapy. The basic circuit includes a blood pump, a membrane lung, and conduit tubing. The gas exchange material in membrane lungs may be solid silicone rubber, a microporous hollow-fiber, or a solid hollow-fiber membrane (16). For most applications, the sweep gas will be 100% oxygen or carbogen (5% CO_2, 95% O_2) at a flow rate equal to the blood flow rate (1:1) (16). The assembled circuit is primed under sterile conditions with an isotonic electrolyte solution resembling normal extracellular fluid. Tubing length and diameter will determine the resistance to blood flow and is chosen to allow free venous drainage and avoid high resistance pressure drop on the blood return side. Vascular access is usually achieved by cannulation of large vessels in the neck or the groin (16). Depending on whether circulatory support is needed or not, two main options are available: Venous-arterial (VA) and veno-venous (VV) ECMO. VA ECMO is used in both blood oxygenation and circulation or only as circulatory support. VV ECMO is indicated for patients with potentially reversible, refractory, life-threatening hypoxemia, or hypercapnia or in patients where acceptable oxygenation or decarboxylation can be obtained only with injurious ventilatory settings (17).

In COVID-19 patients, the respiratory infection manifests in two different stages, with the first week characterized by flu-like symptoms that improve even if the viral load persists, and a recurrent period during the second week in which >20% of patients may require mechanical ventilation due to respiratory failure secondary to diffuse alveolar damage, squamous metaplasia, giant cell infiltrates and increased macrophage levels in the interstitium and the alveoli (18).

While most COVID-19 admissions in the ICU are due to hypoxemic respiratory failure requiring IMV, a significant percentage of patients fail maximal conventional therapies (19). In patients with severe acute respiratory distress syndrome (ARDS) refractory to lung-protective ventilation strategies, initiation of ECMO allows for adequate oxygenation while maintaining safe airway pressures and tidal volume (4). ECMO allows 'ultra-protective ventilation' or 'lung rest' which basically protects against volutrauma and barotrauma by lowering the tidal volume, plateau pressure and the driving pressure and decreases the occurrence of ventilator-induced lung injury (4). It can also contribute to the prevention of subsequent multi-organ failure (20).

ECMO has been used for ARDS since 1972 (21). However, it was in the context of the 2009 H1N1 influenza epidemic that its usage increased, with conventional ventilatory support vs. ECMO for a severe adult respiratory failure (CESAR) multicenter randomized controlled trial, revealing an ECMO-based management protocol to significantly improve survival without severe disability in adult patients with severe but potentially reversible respiratory failure (22).

4. ECMO use in the management of critically ill COVID-19 patients: Current guidelines

The pandemic determined an intense scientific endeavor reflected by the publication of clinical guidelines for the management of patients with COVID-19 by the World Health Organization (WHO) (23), the Centers for Disease Control and Prevention (CDC) (24), the Extracorporeal Life Support Organization (ELSO) (19,25) and the American Society for Artificial Internal Organs (ASAIO) (26), including recommendations for the use of ECMO in the management of COVID-19 patients.

ECMO should be considered to support severe COVID-19 pulmonary infections in patients with advanced respiratory failure, failing prone positioning maneuvers, and maximal ventilatory therapy, who are otherwise reasonable candidates based upon current risk assessment scoring systems (27). Patients without comorbid conditions under the age of 50 are the highest priority, respecting standard contraindications such as: terminal diseases, highly limited life expectancy at baseline, active biochemical or clinical coagulopathy, major central nervous system damage, and the absence of consent (26). According to the ASAIO recommendations, the decision to utilize ECMO, relates to anticipated benefit (failure of mechanical ventilation to achieve adequate oxygenation, or requirement of traumatic mechanical ventilation settings in order to achieve adequate oxygenation) in the background of organ systems not directly supported or treated by ECMO, risks (most notably, local cannulation-related complications, and active or biochemical coagulopathy), ECMO supply availability and other institutional infrastructure, and practitioner expertise (26). Furthermore, it is suggested to implement ECMO after a clear failure of IMV, paralytic agents, and prone positioning restricted to those with isolated pulmonary dysfunction who are invasively mechanically ventilated ≤7 days (26). While ECMO is warranted when metrics indicate a high (80%) risk of mortality with conventional management, no lung or cardiac recovery after 14 days on ECMO can largely be considered futile and the patient can be returned to conventional management (26).

5. Worldwide data regarding ECMO-supported COVID-19 patients

The worldwide use of ECMO has increased steadily as the pandemic evolved. From 202 published cases by August 2020 (28), the number of ECMO-supported COVID-19 patients reached 5,079 cases by March 1, 2021, with 3,794 patients who initiated ECMO at least 90 days previously (93% VV ECMO, 48% in hospital mortality) (29). The updated worldwide registry of COVID-19 patients who received ECMO can be accessed online on the ELSO website (29).

Yang *et al* reported data from 73 COVID-19 patients treated with ECMO in 21 ICUs in Hubei, China between January 6 to March 27, 2020 (median age 62 years, 63% male) (30). The median duration of ECMO support was 18.5 days (30). Since ECMO initiation, the 30- and 60-day mortality were 63.0 and 80.8%, respectively with no significant difference on mortality between ECMO-supported COVID-19 patients and COVID-19 patients treated with IMV only (80.8 vs. 71.2%) (30).

Barbaro *et al* reported data from the International ELSO Registry of 1,035 patients with COVID-19 who received ECMO support between January 16 and May 1, 2020, at 213 hospitals in 36 countries (mean age 49 years, 74% male) (28). A total of 99% underwent IMV (28). At 90 days follow-up, out of the 1,035 patients on ECMO, 588 (57%) were discharged alive from the hospital, 56 (5%) remained in the ICU, 11 (1%) remained in the hospital, discharged from the ICU and 380 (37%) patients had succumbed (28). The estimated cumulative incidence of in-hospital mortality 90 days after the initiation of ECMO was 37.4% (28). In a subset of 779 patients receiving VV ECMO and characterized as having ARDS (mean age 50 years, 74% male) the estimated in-hospital mortality 90 days after ECMO initiation was 38% with recommendation to consider ECMO in refractory COVID-19-related respiratory failure in experienced centers (28).

Rieg *et al* reported data from 213 patients with laboratory-confirmed COVID-19 hospitalized in one of the largest ARDS and ECMO referral centers in Germany between February 25, and May 8, 2020 (median age 65 years, 61% male) (31). A total of 70 (33%) patients were admitted to the ICU, of which 57 (81%) patients received IMV and 23 patients ECMO support (31). Medical treatment included lopinavir/ritonavir (54 patients), hydroxychloroquine (92 patients), remdesivir (1 patient), and tocilizumab (7 patients) (31). At 7 weeks follow-up, 161 (75.6%) patients were discharged alive, and 51 (23.8%) patients had succumbed. The probabilities of mortality were 16% if the patient was initially on a regular ward, 47% if in the ICU and 57% if mechanical ventilation was required at study entry (31).

Shaefi *et al* reported data from 190 ECMO-supported patients within 14 days of ICU admission, between March 1 and July 1, 2020, using data from a multicenter cohort study of 5,122 critically ill adults with COVID-19 admitted to 68 hospitals across the United States (median age 49 years, 72,1% male) (32). At 60 days follow-up, 94 (49.5%) patients were discharged, 33 (17.4%) remained hospitalized and 63 (33.2%) patients had succumbed (32). Patients who received ECMO had lower mortality than those who did not (32).

Zhang *et al* reported data from 43 consecutive patients with COVID-19 who received VV-ECMO between March 3 and May 2, 2020, in London (median age 46 years, 76.7% male) (17). A total of 79.1% received immunomodulation with methylprednisolone for persistent maladaptive hyperinflammatory state. A total of 14 (32.6%) patients succumbed and 29 (67.4%) survived to hospital discharge with a median duration of 13 days on VV-ECMO (17).

Schmidt *et al* reported data from 83 patients who received ECMO for COVID-19-associated ARDS in 5 ICUs in the Paris-Sorbonne University Hospital Network, between March 8 to May 2, 2020 (median age 49 years, 73% male) (33). At 60 days follow-up, 48 (57.8%) patients were alive and discharged from the ICU, 5 (6%) were alive and still in the ICU and 30 patients had succumbed (36.1%) (33).

Herrmann *et al* reported data from 106 patients admitted to the ICUs for COVID-19-induced ARDS from 5 German secondary or tertiary hospitals between March 12 and May 4, 2020 (34). Survival of ICU treatment was 65% (34). VV ECMO was used in 17 (16.3%) patients and 6 (35.3%) patients survived until ICU discharge (34).

Jacobs *et al* reported data from 32 consecutive patients with COVID-19 who were placed on ECMO therapy provided by Specialty Care for severe respiratory failure refractory to conventional management, at 9 different hospitals in United States between March 17, 2020, and April 9, 2020 (median age 52.4 years, 68.8% male) (35). At the cutoff data for the study, 17 (53.1%) patients remained on ECMO, 10 (31.2%) had succumbed, and 5 (15.6%) were alive and extubated after removal from ECMO. Adjunctive medication in the surviving patients while on ECMO was as follows: A total of four out of the five survivors received intravenous steroids, three out of the five survivors received antiviral medications (remdesivir), two out of the five survivors were treated with anti-interleukin-6-receptor monoclonal antibodies (tocilizumab or sarilumab), and one out of the five survivors received hydroxychloroquine (35).

Zhu *et al*, in a systematic review and meta-analysis (867 patients included until May 2020), revealed that, compared with mechanical ventilation therapy alone, ECMO therapy significantly reduced the mortality at 90 days and at 30 and 60 days with device-related adverse events similar between the ECMO group and IMV alone group (36).

6. Discussion

The available worldwide published data from inception of the pandemic until the beginning of March 2021 revealed that 14 to 17% of hospitalized patients with COVID-19 became critically ill (9,12,13).

There is a heterogeneity of published data regarding the outcomes of critically ill COVID-19 patients. These differences may be due to diverse referral strategies, variable local pressure on health care systems leading to restrictions in care and triage of patients, different availability of ICU, IMV and ECMO capacities which may influence admission strategies and decisions on treatment withdrawal (31) but also due to variable follow-up. Guan *et al* (9) reported an 8.1% mortality rate of COVID-19 critically ill patients but 89% of the patients were still hospitalized at the cutoff data for the study which can drastically influence the 30-, 60- or 90-days mortality. Similarly, Grasselli *et al* reported a 26% ICU mortality after 7 days of follow-up while 58% of patients were still receiving care in the ICU (11). Docherty *et al* reported a 32% mortality rate after 14 days of follow-up while 41% of patients were still in the ICU (12).

Furthermore, it is mandatory to interpret the available published data in the larger context of availability of ECMO around the world. ECMO use is restricted to specific centers and requires a highly trained team with a patient: nurse ratio of 1:1 (19) which can be particularly challenging in the limited resources of a pandemic. There are 979 centers for ECMO worldwide (329 in the United States, 26 in Australia, 20 in the United Kingdom, 121 in Europe, 26 in Germany, 15 in Italy and 13 in Spain) according to the Extracorporeal Life Support Organization with few Centers of Excellence in Europe (37,38).

There is however a consensus regarding the high percentage of COVID-19 critically ill patients admitted to the ICU who require IMV. A total of 75.8 to 88.1% of ICU admitted patients underwent IMV (9,11,13,29) and the mortality rates of COVID-19 critically ill patients admitted to the ICU who underwent IMV reached 88.1% (13).

It must be emphasized that ECMO support is a strategy employed only in critically ill patients, who are already under IMV that is initiated when metrics indicate 80% risk of mortality with conventional management (19). Similar to the cardio-pulmonary by-pass in open heart surgery, ECMO is not a treatment but a life support technique that keeps the patient alive when lung, heart or both are failing, giving time for the patient to recover and benefit from a causal treatment with particular importance in the context of new emerging therapies for the disease (39).

Data from studies with 60 to 90 days follow-up showed that the 60-day mortality of critically ill COVID-19 patients who underwent IMV and benefited from ECMO support ranged from 33.2 to 36.1% (32,33), with a 90-day mortality rate of 37% (28).

7. Conclusions

The use of ECMO in the management of critically ill patients with COVID-19-induced ARDS refractory to conventional mechanical invasive ventilation is increasing. By increasing the survival rate from <20 to >50%, ECMO proved to be a valuable resource in the management of the most challenging critically ill COVID-19 patients when properly selected.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

AFP analyzed the data, made substantial contributions to conception and design, and was involved in drafting the manuscript. CEP made substantial contributions to the analysis and interpretation of data and was involved in drafting the manuscript. IBB interpreted the data, made substantial contributions to the acquisition of the data, revising the manuscript critically for important intellectual content. MCV and AB interpreted the data, made substantial contributions to the acquisition of the data, and were involved in drafting the manuscript. AȚ analyzed the data, made substantial contributions to analysis and interpretation of data, revising the manuscript critically for important intellectual content. GT analyzed the data, made substantial contributions to conception and design, revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, *et al*: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395: 497-506, 2020.
2. WHO. WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
3. Report of World Health Organization. Available at https://covid19.who.int/ Accessed on 2 March 2021.
4. Ahmed T, Ahmed T, Karimi H, Tolle L and Iqbal MN: COVID19 Acute respiratory distress syndrome and extra-corporeal membrane oxygenation; A mere option or ultimate necessity. Perfusion 36: 559-563, 2021.
5. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, Cuomo-Dannenburg G, Thompson H, Walker PGT, Fu H, *et al*: Estimates of the severity of coronavirus disease 2019: A model-based analysis. Lancet Infect Dis 20: 669-677, 2020.
6. Boban M: Novel coronavirus disease (COVID-19) update on epidemiology, pathogenicity, clinical course and treatments. Int J Clin Pract 75: e13868, 2021.
7. Weber AG, Chau AS, Egeblad M, Barnes BJ and Janowitz T: Nebulized in-line endotracheal dornase alfa and albuterol administered to mechanically ventilated COVID-19 patients: A case series. Mol Med 26: 91, 2020.
8. Ma X, Liang M, Ding M, Liu W, Ma H, Zhou X and Ren H: Extracorporeal membrane oxygenation (ECMO) in critically ill patients with coronavirus disease 2019 (COVID-19) pneumonia and acute respiratory distress syndrome (ARDS). Med Sci Monit 26: e925364, 2020.
9. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, *et al*: Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 382: 1708-1720, 2020.
10. Liang WH, Guan WJ, Li CC, Li YM, Liang HR, Zhao Y, Liu XQ, Sang L, Chen RC, Tang CL, *et al*: Clinical characteristics and outcomes of hospitalised patients with COVID-19 treated in Hubei (epicentre) and outside Hubei (non-epicentre): A nationwide analysis of China. Eur Respir J 55: 2000562, 2020.
11. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, *et al*: Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the lombardy region, Italy. JAMA 323: 1574-1581, 2020.
12. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G, *et al*: Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: Prospective observational cohort study. BMJ 369: m1985, 2020.
13. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; The Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, *et al*: Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. JAMA 323: 2052-2059, 2020.
14. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, Rosser EC, Webb K and Deakin CT: Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun 11: 6317, 2020.
15. Hu BS, Hu MZ, Jiang LX, Yu J, Chang Y, Cao Y and Dai ZP: Extracorporeal membrane oxygenation (ECMO) in patients with COVID-19: A rapid systematic review of case studies. Eur Rev Med Pharmacol Sci 24: 11945-11952, 2020.
16. ELSO Guidelines for Cardiopulmonary Extracorporeal Life Support Extracorporeal Life Support Organization, Version 1.4 August 2017 Ann Arbor, MI, USA (www.elso.org). Accessed at March 2 2021.
17. Zhang J, Merrick B, Correa GL, Camporota L, Retter A, Doyle A, Glover GW, Sherren PB, Tricklebank SJ, Agarwal S, *et al*: Veno-venous extracorporeal membrane oxygenation in coronavirus disease 2019: A case series. ERJ Open Res 6: 00463-2020, 2020.
18. Docea AO, Tsatsakis A, Albulescu D, Cristea O, Zlatian O, Vinceti M, Moschos SA, Tsoukalas D, Goumenou M, Drakoulis N, *et al*: A new threat from an old enemy: Re-emergence of coronavirus (review). Int J Mol Med 45: 1631-1643, 2020.
19. Shekar K, Badulak J, Peek G, Boeken U, Dalton HJ, Arora L, Zakhary B, Ramanathan K, Starr J, Akkanti B, *et al*: Extracorporeal life support organization coronavirus disease 2019 interim guidelines: A consensus document from an international group of interdisciplinary extracorporeal membrane oxygenation providers. ASAIO J 66: 707-721, 2020.
20. Lim JKB, Qadri SK, Toh TSW, Lin CB, Mok YH and Lee JH: Extracorporeal membrane oxygenation for severe respiratory failure during respiratory epidemics and pandemics: A narrative review. Ann Acad Med Singap 49: 199-214, 2020.
21. Hill JD, O'Brien TG, Murray JJ, Dontigny L, Bramson ML, Osborn JJ and Gerbode F: Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. N Engl J Med 286: 629-634, 1972.
22. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, *et al*: Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomised controlled trial. Lancet 374: 1351-1363, 2009.
23. World Health Organization: Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance. March 3, 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf. Accessed at March 1, 2021.
24. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19), updated Feb.16, 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. Accessed at March 1, 2021.
25. Badulak J, Antonini MV, Stead CM, Shekerdemian L, Raman L, Paden ML, Agerstrand C, Bartlett RH, Barrett N, Combes A, *et al*: Extracorporeal membrane oxygenation for COVID-19: Updated 2021 guidelines from the extracorporeal life support organization. ASAIO J 67: 485-495, 2021.

26. Rajagopal K, Keller SP, Akkanti B, Bime C, Loyalka P, Cheema FH, Zwischenberger JB, El Banayosy A, Pappalardo F, Slaughter MS and Slepian MJ: Advanced pulmonary and cardiac support of COVID-19 patients: Emerging recommendations from ASAIO-A 'living working document'. ASAIO J 66: 588-598, 2020.
27. Stawicki SP, Jeanmonod R, Miller AC, Paladino L, Gaieski DF, Yaffee AQ, De Wulf A, Grover J, Papadimos TJ, Bloem C, *et al*: The 2019-2020 novel coronavirus (severe acute respiratory syndrome coronavirus 2) pandemic: A joint American college of academic international medicine-world academic council of emergency medicine multidisciplinary COVID-19 working group consensus paper. J Glob Infect Dis 12: 47-93, 2020.
28. Barbaro RP, MacLaren G, Boonstra PS, Iwashyna TJ, Slutsky AS, Fan E, Bartlett RH, Tonna JE, Hyslop R, Fanning JJ, *et al*: Extracorporeal membrane oxygenation support in COVID-19: An international cohort study of the extracorporeal life support organization registry. Lancet 396: 1071-1078, 2020.
29. Extracorporeal Life Support Organization. ECMO in Covid-19, https://www.elso.org/Registry/FullCOVID19 RegistryDashboard.aspx. Accessed at March 2, 2021.
30. Yang X, Hu M, Yu Y, Zhang X, Fang M, Lian Y, Peng Y, Wu L, Wu Y, Jun Y, *et al*: Extracorporeal membrane oxygenation for SARS-CoV-2 acute respiratory distress syndrome: A retrospective study from Hubei, China. Front Med (Lausanne) 7: 611460, 2021.
31. Rieg S, von Cube M, Kalbhenn J, Utzolino S, Pernice K, Bechet L, Baur J, Lang CN, Wagner D, Wolkewitz M, *et al*: COVID-19 in-hospital mortality and mode of death in a dynamic and non-restricted tertiary care model in Germany. PLoS One 15: e0242127, 2020.
32. Shaefi S, Brenner SK, Gupta S, O'Gara BP, Krajewski ML, Charytan DM, Chaudhry S, Mirza SH, Peev V, Anderson M, *et al*: Extracorporeal membrane oxygenation in patients with severe respiratory failure from COVID-19. Intensive Care Med 47: 208-221, 2021.
33. Schmidt M, Hajage D, Lebreton G, Monsel A, Voiriot G, Levy D, Baron E, Beurton A, Chommeloux J, Meng P, *et al*: Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: A retrospective cohort study. Lancet Respir Med 8: 1121-1131, 2020.
34. Herrmann J, Adam EH, Notz Q, Helmer P, Sonntagbauer M, Ungemach-Papenberg P, Sanns A, Zausig Y, Steinfeldt T, Torje I, *et al*: COVID-19 induced acute respiratory distress syndrome-a multicenter observational study. Front Med (Lausanne) 7: 599533, 2020.
35. Jacobs JP, Stammers AH, St Louis J, Hayanga JWA, Firstenberg MS, Mongero LB, Tesdahl EA, Rajagopal K, Cheema FH, Coley T, *et al*: Extracorporeal membrane oxygenation in the treatment of severe pulmonary and cardiac compromise in coronavirus disease 2019: Experience with 32 patients. ASAIO J 66: 722-730, 2020.
36. Zhu Y, Zhang M, Zhang R, Ye X and Wei J: Extracorporeal membrane oxygenation versus mechanical ventilation alone in adults with severe acute respiratory distress syndrome: A systematic review and meta-analysis. Int J Clin Pract 75: e14046, 2021.
37. Extracorporeal Life Support Organization. https://www.elso.org/Registry/SupportDocuments/CenterIDList.aspx. Accessed at March 2, 2021.
38. Extracorporeal Life Support Organization. https://www.elso.org/Membership/CenterMap.aspx. Accessed at March 2, 2021.
39. Calina D, Docea AO, Petrakis D, Egorov AM, Ishmukhametov AA, Gabibov AG, Shtilman MI, Kostoff R, Carvalho F, Vinceti M, *et al*: Towards effective COVID-19 vaccines: Updates, perspectives and challenges (review). Int J Mol Med 46: 3-16, 2020.