

Reviewer#1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors:

Pathophysiology section: Please, add an explanation about how severely ill patients develop end stage disease and die because of the virus. This is an important consideration because, the main issue of the review is ventilator support, but without considering what happens in other organs while other therapies do their job.

A sentence was added to the last paragraph of the pathophysiology section better stating the cause of death in patients with critical disease.

Rationale of ECMO section: ECMO intends to improve lung gas exchange while other therapies do the same in other organs. Please, add comments about specific considerations in cardiovascular, renal and other supports while ECMO is working.

Several sentences were added to the bottom of the 4th paragraph describing the use of CRRT in patients on ECMO who develop kidney injury pre-renal. This is consistent with the rest of the paragraph that discusses cardiovascular compromise that may develop in patients on ECMO.

At the same time, please, explain ECMO usefulness in other critical respiratory failures. For example, it appears that ECMO does not add value to Adult Respiratory Distress Syndrome (ARDS) as reported by Combes et al in NEJM in 2018 (N Engl J Med. 2018 May 24; 378(21):1965-1975. doi: 10.1056/NEJMoa1800385). These data can improve our rationale about if it is convenient to work in introducing ECMO to care patients severely ill because of Covid-19.

A sentence was added at the beginning of the 6th paragraph under “Rationale for using ECMO in COVID-19 Patients” stating Combes et al showed ECMO did not lower 60-day mortality in patients with severe ARDS from non-COVID-19 causes prior to COVID-19. This was added in attempt to lend context that prior to COVID-19, ECMO was far from a “saving-grace” and data is sparse for COVID-19 patients now that the pandemic is upon us.

How many patients do the authors think will be candidates to use ECMO? For example, from the early American, experience published in MMWR on March 27th 2020, 5-11% of Covid patients go to an ICU and one third of those finally die (1-3% of all hospitalized patients), presumably with respiratory and multiorgan failure. This number is the core of the problem, because as the authors point, it is necessary to comply with a series of requisites to implement ECMO.

Unfortunately, it is very difficult to assess the number of patients that will qualify for ECMO with such little data and guideline support. However, the reviewer raises an interesting point about compliance with requisites. As a result, two sentences were added under “Referral Systems” (Special Considerations for ECMO Use in COVID-19 Patients) that discusses a need for strict criteria to consider benefit versus futility, and when a patient should be eligible for ECMO before futility becomes imminent.

Reference 15 (Extracorporeal Life Support Organization (ELSO). June 6 2020) is not clear to describe the 55% survival rate after ECMO. Could it be that those patients were less sick than those intended to put in ECMO as Table 1 point out?

We agree this was confusing as “survival rate” and “discharged alive rate” were mentioned in 2 different places. The “survival rate” was removed as it was inappropriately discussed in the “rationale for ECMO section” and is confusing as there are many factors that could skew that number, to the reviewer’s point. However, the 55% discharge alive rate refers to the rate at 90 days from ECMO which explains the higher-than-expected rate than say, 30 days from ECMO. It also refers to those who are discharged to rehab and LTAC facilities indicating a possibility lengthier recovery. This sentence and explanation were added under the 2nd paragraph under “Current Utilization of ECMO” to better clarify.

In this same line of thinking. Please comment about the cost of implementing ECMO or designing a referral system to send eventual candidates for ECMO and from the ethical point of view, how that figure compares with opening new critical care beds with classic equipment for respiratory and other organs support.

The last paragraph was better elaborated on the ethical dilemma of supporting traditional non-invasive and invasive mechanical ventilation in lesser equipped areas at the cost of the critically ill that may benefit from ECMO, due to the cost of implementing ECMO.

How do the author reconcile their point of view about ECMO in Covid-19 with ELSO recommendation: “There are insufficient data to recommend either for or against the routine use of extracorporeal membrane oxygenation (ECMO) for patients with COVID-19 and refractory hypoxemia” (<https://www.covid19treatmentguidelines.nih.gov/critical-care/>).

A sentence was added at the bottom of the 6th paragraph under “Rationale for ECMO” section that states the ELSO currently does not recommend for or against ECMO in patients with COVID-19 due to insufficient data, consistent with the message already described in that paragraph. Given that this is a stance that is not in favor for or against ECMO, our viewpoint about ECMO in COVID-19 patients throughout the manuscript does not change.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The spread of coronavirus disease 2019 (COVID-19) continues to grow exponentially in most countries, posing an unprecedented burden on the healthcare sector and the world economy. Unfortunately, there is no effective medication other than comprehensive support. However, the mild type of COVID-19 patients can recover shortly after appropriate clinical intervention. The moderate type patients, especially the elderly or the ones with comorbidity, can worsen and become severe, indicating high mortality rate. The mortality in mechanically ventilated COVID-19 patients remains high, and it is unclear if some of these patients may be rescued with ECMO. This review is mainly introduced from the following aspects: Rationale for using Extracorporeal Membrane Oxygenation (ECMO) in COVID-19

Patients, Special Considerations for ECMO Use in COVID-19 Patients, and Future of ECMO Use. In conclusions, ECMO remains a valid treatment option for patients when other conventional treatment strategies fail. I think that although ECMO has a role in critically ill patients, there is currently inadequate data to determine the efficacy, optimal patient selection and management on ECMO. It is essential that we learn and understand throughout the current pandemic, in order determine the risk-benefit ratio of ECMO in COVID-19.

Thank you for the remarks! We appreciate your recommendation to accept the manuscript.

5 EDITORIAL OFFICE'S COMMENTS

Nevertheless, the authors need to add some comments to clarify several issues like how severely ill patients develop end stage disease and die because of the virus.

Sentence added at the bottom of the last paragraph under “Pathophysiology of SARS-CoV-2 Virus” better stating the cause of death in patients with critical disease.

The authors also need to add specific considerations into other supports working in parallel with ECMO and improve the rationale for using ECMO in other critical respiratory failures.

The first paragraph under “Rationale for ECMO” was refined to include indications for ECMO for those who do not have ARDS from COVID-19. Furthermore, several sentences were added to the bottom of the 4th paragraph describing the use of CRRT in patients on ECMO who develop kidney injury pre-renal. This is consistent with the rest of the paragraph that discusses cardiovascular compromise that may develop in patients on ECMO. Lastly, the second paragraph was refined to discuss the outcomes of ECMO in patients who are not being treated for COVID-19 for comparison of outcomes to those being treated with COVID-19.

The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the CrossCheck detection and Bing search.

The forms have been signed and uploaded to the submission system.

I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor

The original Figures have been uploaded as powerpoint files and should be fully editable as requested.

I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references.

The references have been re-formatted per this request.

Please revise throughout, the author should put the in-text citations (superscripted) before the punctuation or after the cited author's name, with no spaces

The in-text citations have been fixed.

Please provide the audio core tip file where the content of core tip is recorded;

The audio Core tip has been provided

Please provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement

These forms have been uploaded