

Dear Reviewers and Editor

RE: Manuscript NO: 61232

Title: Awake extracorporeal membrane oxygenation support for a critically ill COVID-19 patient: A case report and literature review

We would like to thank World Journal of Clinical Cases for giving us the opportunity to revise our manuscript. We thank the Reviewer and Editor for the time and effort spent in reviewing the previous version of the manuscript. We have taken their careful and thoughtful comments into consideration in revising our manuscript. Based on the instructions provided in your letter, we uploaded the file of the revised manuscript. Please find my revisions/corrections in the re-submitted files with all the changes highlighted by using the track changes mode in Word and feel free to contact us for any issue.

Best wishes, Tong Li, MD, Professor,

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## **Replies to Reviewer's Comments:**

### **Reviewer #1:**

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

1. Introduction: Line 7 and 8: "Some COVID-19 patients experience mild symptoms, and there is no obvious abnormality in chest CT, while a few patients get severe respiratory failure quickly". Why?
2. Line 12, 18: please explain the mean of ARDS, CESAR, PPV.
3. Line 18: "According to some reports..." (the author only cites a single reference). please cite these reports.
4. Line 21, 22: "with extremely high mortality" please provide a recent statistic for mortality rate. It is interesting to write about the mechanism of virus action, target cells and the treatment plan for patients. Case report. It is interesting to provide more information about the case history.
5. Discussion Line 6: Please explain NIV
6. Line 21: "Two recent meta-analyses showed" the author cites one reference only.
7. Line 15, 16: "Some studies proved that for severe patients, as the use time of ECMO increases, the risk of bleeding will rise at the same time" Please cite these studies.
8. Line 17: Please write the mean of APTT.
9. Note: the manuscript needs language editing and proofread

### **Answer:**

Thank you very much for the comments.

1. Introduction: Line 7 and 8: "Some COVID-19 patients experience mild symptoms, and there is no obvious abnormality in chest CT, while a few patients get severe respiratory failure quickly". Why?

**Answer:** Different variants of SARS-CoV-2 showed different pathogenic intensities, and the relationship between genotype and phenotype was preliminarily

established. It is revealed from the side that COVID-19 patients show a variety of clinical symptoms from gradual to death. In addition to being affected by age, complications, etc., it may also be due to carrying different variants of SARS-CoV-2. (Reference: Yao H, Lu X, Chen Q, Xu K, Chen Y, Cheng M, Chen K, Cheng L, Weng T, Shi D, Liu F, Wu Z, Xie M, Wu H, Jin C, Zheng M, Wu N, Jiang C, Li L. Patient-derived SARS-CoV-2 mutations impact viral replication dynamics and infectivity in vitro and with clinical implications in vivo. *Cell Discov.* 2020 Oct 29;6(1):76. doi: 10.1038/s41421-020-00226-1. PMID: 33298872; PMCID: PMC7595057.)

2. Line 12, 18: please explain the mean of ARDS, CESAR, PPV.

**Answer:** We have supplemented the explanation in the manuscript. **ARDS** (Acute Respiratory Distress Syndrome); **CESAR** (A multi-centre randomised controlled trial (CESAR) was funded in the UK to compare care including ECMO with conventional intensive care management. Reference: Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D; CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet.* 2009 Oct 17;374(9698):1351-63. doi: 10.1016/S0140-6736(09)61069-2. Epub 2009 Sep 15. Erratum in: *Lancet.* 2009 Oct 17;374(9698):1330. PMID: 19762075.); **PPV** (Prone Position Ventilation)

3. Line 18: "According to some reports..." (the author only cites a single reference). please cite these reports.

**Revise:** Add references " Voelker MT, Jahn N, Bercker S, Becker-Rux D, Köppen S, Kaisers UX, Laudi S. Bauchlagerung von Patienten an der venovenösen ECMO ist möglich und sicher [Prone positioning of patients during venovenous extracorporeal membrane oxygenation is safe and feasible]. *Anaesthesist.* 2016 Apr;65(4):250-7. German. DOI: 10.1007/s00101-015-0131-6. PMID: 27007777."

4. Line 21, 22: "with extremely high mortality" please provide a recent statistic for mortality rate. It is interesting to write about the mechanism of virus action, target

cells and the treatment plan for patients Case report It is interesting to provide more information about the case history.

**Revise:** The recent statistic for COVID-19 mortality rate is 2.16%. We made changes in the manuscript. We added a part to the discussion section” Classified in the Coronaviridae family and betacoronavirus genus, SARS-CoV-2 is the seventh coronavirus known to infect humans. Coronaviruses are enveloped positive-sense, single-stranded RNA viruses with mammalian and avian hosts. The SARS-CoV-2 virion is composed of a helical capsid formed by nucleocapsid (N) proteins bound to the RNA genome and an envelope made up of membrane (M) and envelope (E) proteins, coated with trimeric spike (S) proteins. The S protein binds to the ACE2 enzyme on the plasma membrane of type 2 pneumocytes and intestinal epithelial cells. After binding, the S protein is cleaved by a host membrane serine protease, TMPRSS2, facilitating viral entry.

Multiple clinical trials are underway to define potential roles for antiviral agents and specific immunomodulators. Antiviral agents under investigation include inhibitors endosome maturation (hydroxychloroquine), inhibitors of viral RNA-dependent RNA polymerase (remdesivir, favipiravir) and inhibitors of viral protein synthesis and maturation (lopinavir/ritonavir); immunomodulators under investigation include interferon- $\beta$  and blockade of IL-6 receptor or IL-6 (tocilizumab, siltuximab, sarilumab). Passive immunization with convalescent plasma and active immunization strategies involving live-attenuated virus, chimeric virus, subunit, nanoparticle, RNA, and DNA are in development and testing.”

5. Discussion Line 6: Please explain NIV

**Answer:** NIV (Non-invasive ventilation).

6. Line 21: “Two recent meta-analyses showed” the author cites one reference only.

**Revise:** Add references “Sud S, Sud M, Friedrich JO, Adhikari NK. Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. CMAJ. 2008 Apr 22;178(9):1153-1161. DOI: 10.1503/cmaj.071802. PMID: 18427090.”

7. Line 15, 16: “Some studies proved that for severe patients, as the use time of ECMO increases, the risk of bleeding will rise at the same time” Please cite these studies.

**Revise: Add references** “Ellouze O, Abbad X, Constandache T, Missaoui A, Berthoud V, Daily T, Aho S, Bouchot O, Bouhemad B, Guinot PG. Risk Factors of Bleeding in Patients Undergoing Venous Arterial Extracorporeal Membrane Oxygenation. *Ann Thorac Surg.* 2021 Feb;111(2):623-628. DOI: 10.1016/j.athoracsur.2020.02.012. PMID: 32171730.” **Another references** “Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, Da Silva D, Zafrani L, Tirot P, Veber B, Maury E, Levy B, Cohen Y, Richard C, Kalfon P, Bouadma L, Mehdaoui H, Beduneau G, Lebreton G, Brochard L, Ferguson ND, Fan E, Slutsky AS, Brodie D, Mercat A; EOLIA Trial Group, REVA, and ECMONet. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. *N Engl J Med.* 2018 May 24;378(21):1965-1975. DOI: 10.1056/NEJMoa1800385. PMID: 29791822.”

8. Line 17: Please write the mean of APTT.

**Answer:** We have added content in the manuscript (the mean of APTT was  $48.5 \pm 5.3$ )

9. Note: the manuscript needs language editing and proofread

**Answer:** The manuscript has been rewritten in accordance with the Guidelines for Manuscript Preparation. We revised the grammar of the article again.