

Peer review file

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Reviewer A

This manuscript describes the different clinical course of first wave and second wave COVID patients on vvECMO.

The objective is clear however the conclusions are difficult as only 20 patients both arms are included.

Major comments:

Comment 1:

Number of patients is too low to draw any conclusion considering trend of clinical course or outcome.

Reply 1:

Dear Reviewer A, thank you for the response and we appreciate your comments. Indeed, 39 patients do not allow for outcomes analysis with statistically meaningful results and conclusion. We adjusted the conclusion into a general statement on all patients and only mentioned that we observed less favorable outcomes in the second wave which is similar to the global trend of various registries. Therefore, we changed the conclusion of the abstract and a part of the general conclusions.

Changes in manuscript:

Abstract, Page 2, line 52-54.

Conclusion, Page 13, line 362-365.

Comment 2:

The EuroElso study on COVID is still running, and contains many hundreds of patients. Especially in this light, 20 patients in both arms are extremely low.

Reply 2:

Yes, the ELSO registry is gathering data on a high number of patients and can be used to draw accurate conclusions. Our study sample is small, and we think that the manuscript should focus on other insights of our analysis. In particular, strengths of our study included a detailed description of our patients with a high number of variables,

of which some are not included in other studies. For instance, our study included risk scores, laboratory measurements and blood products. Furthermore, the clinical course and hospitalization before ECMO is described in very detail. The results of our center are representative to what we see in the trends of registries. We could give insights on common issues of patients from the second wave, such as longer periods in the ICU or on mechanical ventilation, and the non-responsiveness to adjuvant therapies (like steroids). Therefore, we highlighted these important factors and changed parts of the introduction, discussion, and conclusion.

Changes in manuscript:

Introduction, Page 4, line 71-72.

Discussion, Page 10-11, line 255-280.

Conclusion, Page 13, line 362-365.

Comment 3:

Many variables are statistically tested, while looking for differences between both waves. Consider correcting for multiple testing.

Reply 3:

Dear Reviewer A, thank you again for this important hint. We agree with Reviewer A, that due to the high number of variables there is a high chance for false positive values, and we did consider correction for multiple testing. However, we think that in an early single center analysis with a small sample size, it is important to present all possible differences with a low threshold. We did not want to miss important findings and have false negatives values which could have been important in the future. A Bonferroni correction would eliminate all significant values.

Nevertheless, you mentioned an important topic which has not been addressed properly in the manuscript. Therefore, we changed the limitations section in the discussion and mentioned possible correction methods and emphasized that there's a good chance that our results included false positive values.

Changes in manuscript:

Discussion, Page 14, line 350-356.

Comment 4:

In section Results, line 224, the authors state that patients in the second wave had a

lower survival with a P value of 0.2. The Kaplan Meijer curve showed a P value of 0.280. So, the P value even approaches 0.3. The authors state in section Results (line 224), as well as in section Discussion (line 260) that mortality was lower in the first wave compared to the second wave. I think that is simply incorrect.

Reply 4:

It is right that the Kaplan-Meier curve showed a p-value of 0.284. I would like to explain our analysis and we will change some parts of the manuscript because it was confusing. There were two different methods to compare survival. The first one was to simply perform the Fisher's Exact test of the categorical variables which revealed a p-value of 0.200 and can be found in Table 3 (Survival until discharge). The second was a log-rank test to compare the estimates of the hazard functions of the two groups at each observed event time. Even though the log-rank test has some advantages because it is time-stratified within 90 days after initiation of ECMO, we think it is more accurate to use the Fisher's Exact test and describe "Survival until discharge" in the Abstract and Discussion. The reason for this decision was based on the fact that we did not follow patients after hospital discharge and the hospital stay of some patients is less than 90 days.

We made the manuscript more explicit and clearly called it survival until discharge in the abstract and results section; and we mentioned in the limitations that we did not follow patients after discharge. Furthermore, we explained that it is not statistically significant, but clinically relevant in the discussion.

Changes in text:

Abstract, Page 2, line 41-42.

Results, Page 9, line 223.

Discussion, Page 10, line 238-244.

Reviewer B

Comment: Although you wrote the manuscript well, I cannot find any distinguishing features of your data, compared to other studies. It seems that you just described some differences in outcomes between the first and the second wave.

And, although the number of EMCO patients is usually not large in many studies, the number of patients in the manuscript was too small to draw a conclusion.

I think, it will be better to change the point of the manuscript and to enroll more patients.

Reply:

Dear Reviewer B, thank you for your valuable comments and effort in reviewing our manuscript. It is true that we did not perform a specific analysis focusing on one special subject. This was not the aim of our study. We rather aimed to describe and share our findings, experiences, and outcomes in detail, as a center offering ECMO-support for critically ill COVID-19 patients throughout the first and second wave. We describe our findings from the first and second wave, because of a possible negative trend which was reported in different registries. We reported some differences in outcomes between the two waves, which are in accordance with the recently published results from large registries. We agree with reviewer B, that one of the study's major limitations is the small number of patients included. On the other hand, the number of COVID-19 patients, who received ECMO-support in our center is a fair number for a single center considering the nature of the disease. Nevertheless, we absolutely agree with Reviewer B, that the design of our study and the small number of patients included, do not justify the making of absolute conclusions. According to Reviewer B, we made changes in the way of results presentation and the conclusions. We also highlighted the limitations that we mentioned.

Changes in text:

Abstract, Page 2, line 52-54.

Discussion, Page 14, line 350-356.

Conclusion, Page 13, line 362-365.

Reviewer C

In their manuscript "Extracorporeal Membrane Oxygenation in Patients with COVID-19: 1-year Experience" Dr. Kersten and colleagues report the results of their retrospective analysis exploring outcomes with ECMO in COVID-19 over two separate phases. Authors found significantly higher rates of adverse outcome during the second wave without a corresponding difference in baseline characteristics. They conclude with words of caution about using ECMO in COVID-19.

The topical area is interesting and the authors should be commended for observing a trend in outcomes over time. The sample size is unfortunately very small which

significantly limits any postulations on the data. This should be emphasized in the manuscript more than it already has. Additional notes include:

Comment 1:

Aims are noted but a hypothesis is not. Authors should note a study hypothesis in the introductory paragraph

Reply 1:

Dear Reviewer C, thank you for your valuable comments and suggestions, which helped us in improving our manuscript. We agree that the major limitation of our study is the small number of patients analyzed. We did re-emphasize this limitation in the Discussion-section.

Dear Reviewer C, thank you for this important note regarding the hypothesis of the study. Our study had the following aims (1) describe our experience of ECMO therapy in patients with COVID-19 after 1 year of practice; and (2) compare the baseline characteristics and outcomes between patients of the first and second epidemic waves. We did not formulate a hypothesis regarding worse outcomes of critically ill COVID-19 patients treated with ECMO during the second wave compared to the first epidemic wave. The reason is that we cannot prove or deny a hypothesis with our small sample and single center analysis. As the other reviewers mentioned, our data did not have the power to formulate conclusions on a negative trend and the cause of it. Therefore, we changed parts of the introduction to emphasize the fact that data (of patients from the second wave) is limited and we performed a descriptive analysis. Furthermore, we changed our conclusion into a general statement that we observed less favorable outcomes in the second wave which is similar to the global trend of various registries.

Changes in text:

Abstract, Page 2, line 52-54.

Discussion, Page 14, line 350-356.

Conclusion, Page 13, line 362-365.

Comment 2:

Many centers adjusted their ECMO programs between waves including in the realms of patient selection and management on ECMO. Was this the case for the authors? Either way, this should be discussed in the manuscript

Reply 2:

Our selection procedure of ARDS patients for ECMO was conducted according to the ELSO guidelines and, during the study period, we did not change our protocol for ARDS patients as we reported positive results during the first wave. It is difficult to name a direct cause for worse outcomes, but we outlined some important factors and differences which could have influenced the outcomes. One is late ECMO requests from referring hospitals which resulted in long times in the ICU and on ventilation before ECMO-start. This is known to be a negative predictor for ECMO success. Another factor is that in the second wave patients did not respond to adjuvant therapies, such as steroids, and then were indicated for ECMO. Steroids were used less frequent in the first wave. We added this information in more detail in the discussion.

Changes in text:

Discussion, Page 10-11, line 255-280.

Discussion, Page 12-13, line 310-321.

Comment 3:

Authors note some differences in medical therapy during the two waves (Steroids especially). The literature on steroid use for COVID should be highlighted.

Reply 3:

This is an important topic. Many studies reported positive results with steroids (especially dexamethasone) and in our region it was used more frequently in the second wave. However, patients already received steroids in the days or weeks before we started ECMO therapy. Our data could not show statistical significance, but patients of the second wave underwent long treatments at the ICU and were already immunosuppressed (from steroids) when we started the ECMO. As Broman et al. mentioned, there was a possible selection bias with patients who did not respond to adjuvant therapies, and neither MV or ECMO would be successful. We added literature and highlighted this topic in the discussion.

Changes in text:

Discussion, Page 12-13, line 310-321.

Comment 4:

Median pre-ECMO MV time varies significantly by waves and could very well be the

key driver of differences. This is not highlighted and/or discuss adequately in the results. It should be accompanied by some consideration of MV duration and outcomes in the broader COVID population

Reply 4:

Indeed, we also think that pre ECMO MV times are an important potential cause for different outcomes. Our data showed that a high proportion of the patients had longer ventilation periods than recommended. Especially in the second wave we observed long ICU and MV periods before ECMO. We added important literature from recent studies and large registries in our discussion. Furthermore, we added literature on all patients with COVID-19 who were admitted to the hospital and discussed its relevance for ECMO outcomes. As a center from Germany, we used reports from national databases which showed similarities and differences between the first and second wave of hospitalized COVID-19 patients.

Changes in text:

Discussion, Page 10-11, line 255-280.

Reviewer D

Thank you for giving me the chance to check the article. Your article is ECMO management for critical COVID-19 patients in 1 year experience. It's an interesting to consider about the indication for critical ECMO patients.

But I have some questions.

Comment 1:

According to survival probability, it's not good outcome for critical COVID-19 patients in ECMO. And, it was no significant difference between first wave and second wave, but, in second wave, we can see the bad survival probability in second wave, what do you think about the reasons for the gap?

Reply 1:

Dear Reviewer C, thank you for your valuable comments and suggestions, which helped us in improving our manuscript. We measured the RESP and SOFA score before the initiation of ECMO. The scores from the first wave were comparable to those from the second wave (Table 1). Therefore, we were surprised that the mortality was higher

in the second wave. As a single center, it is difficult to make conclusions on this observation, however, the ELSO and ECMOnet registries showed a similar negative trend. This was the reason to conduct this descriptive study on patients from the first and second wave. It is difficult to name a direct cause for worse outcomes, but we outlined some important factors and differences which could have influenced the outcomes. One is late ECMO requests from referring hospitals which resulted in long times in the ICU and on ventilation before ECMO-start. This is known to be a negative predictor for ECMO success. Another factor is that in the second wave patients did not respond to adjuvant therapies, such as steroids, and then were indicated for ECMO. Steroids were used less frequent in the first wave. Furthermore, we found some different baseline characteristics, such as pH, p_fHb, and PEEP during ventilation. We improved the whole discussion regarding these important factors.

Changes in text:

Discussion, Page 10-13, line 242-345

Comment 2.

In complications, I think that the rate of thrombosis and bleeding is a little bit high. Thromboembolic events occurred in 36% of the patients, and pulmonary artery embolism was the most frequent (21%).

Major bleeding events (MBE) occurred in 62% of the patients. For me, it is so high rate. In general, the rate is not high such as this result. What factor related to the results do you think about?

Reply 2:

Indeed, bleeding complications were high, especially in patients of the second wave. The most obvious explanation is that during the second wave, ECMO runs were very long (median: 24.5 days) and patient suffered from severe sepsis. Especially bleedings in the airway can be seen frequently for this kind of patients.

Regarding thromboembolic events, we agree that this number is high, especially in the first wave. We think that this phenomenon is more prevalent in COVID-19 patients who receive ECMO than patients with other pathologies who receive ECMO. There are multiple studies who reported that (Ripoll 2021, Bemtgen 2020, Autschbach 2021). We elaborated the occurrence of bleeding events in the discussion and mentioned multiple factors.

Changes in text:

Discussion, Page 11-12, line 281-309.

Comment 3.

After ECMO, in this article, kidney failure is frequently occurred. What do you think about the reason? If you have any reason, what should you do the ECMO management from now? Please tell us about the solution.

Reply 3:

We found a high rate of acute kidney failure, especially in patients who were already suffering from chronic kidney disease. The main reasons for this finding are long periods in the hospital or ICU before the initiation of ECMO. Additionally, ECMO runs were long in this cohort (median: 19 (IQR 11-29)). Most of the patients already had acute kidney failure before the start of ECMO, especially in patients who stayed in the ICU of referring hospitals before the ECMO transfer. We think that the most important change for ECMO patients should be the patient selection. An analysis from Karagiannidis et al. showed that we select more patients with pre-existing acute kidney failure for ECMO therapy in Germany than other countries. This complication is strongly related to the long ICU and MC periods due to late ECMO transfers. We think that patient selection should be more critical regarding later ECMO transfers with pre-existing acute kidney failure. Both are known to be important risk factors for ECMO outcomes. We added this important risk factor in our discussion and used recent literature to support the association to higher mortality.

Changes in text:

Discussion, Page 11, line 263-266.

Comment 4.

However, you described the difference for treatment of COVID-19, from cytokine absorption in first wave to corticosteroids in second wave, Is there anything else you changed between the first and second wave? Because, I feel that the second wave is a little worse than the first wave. What do you think about this?

Reply 4:

During the study period, we did not change our general protocol for ARDS patients as we reported positive results during the first wave. It is true that more patients received

steroids in the early hospitalization period because evidence-based recommendations which were published during the first wave. We also found some different baseline characteristics (pre-ECMO) which indicate the opposite. For example, pH and PEEP values indicated more severe illness in first wave patients. We discussed these dubious findings and have some possible explanations. Acidosis in ARDS patients could be due to a therapeutic modality, which is known to have a protective effect against ventilator-associated lung injury. And low PEEP adjustments could indicate less lung compliance, which is associated with mortality in patients with ARDS on ECMO. More details can be found in our discussion section.

Changes in text:

Discussion, Page 12-13, line 310-345.

Reviewer E

Durak et al., conducted a single center, retrospective study describing the institutional experience throughout a year of COVID-19 for patients supported by both VV and VA ECMO. The study highlights an important observation like the correspondence published in the lancet respiratory medicine by EuroElso ([https://doi.org/10.1016/S2213-2600\(21\)00262-9](https://doi.org/10.1016/S2213-2600(21)00262-9)). The study has limitations of the small sample size, single center, and retrospective nature of the study.

Major revisions:

Comment 1:

- The study mention both VV and VA ECMO enrollment. However, the focus on the respiratory management and support by ECMO for refractory COVID-19 associated ARDS. Please either focus on VV ECMO or elaborate on VA component. What are the indications and highlight hemodynamics parameters, vasoactive meds..etc

Reply 1:

In our center, the indication for VA-ECMO does not differ from the ELSO guidelines. Generally, COVID-19 patients need to be managed with VV ECMO due to refractory respiratory failure. In our study, we had only one patient who was indicated for VA-ECMO due to the following reason. This patient was suffering from moderate

respiratory failure and received mechanical ventilation. However, he also developed severe and predominantly right ventricular failure. Therefore, we started VA-ECMO two days after the initiation of MV. We think that both cardiac and respiratory failure in this patient were initiated by COVID-19 disease. After approximately one month, this patient was successfully weaned from ECMO and survived. This was an important experience regarding severely ill COVID-19 patients and we would not like to exclude this patient. However, it is true that we did not elaborate this patient adequately in the text. Therefore, we added information in the results section.

Changes in text:

Results, Page 7, line 166-168.

Results, Page 8, line 214-215.

Comment 2:

- Please mention the cause of death in the non-survivors. Is it different between the first and the second wave?

Reply 2:

Cause of death was multi organ failure in all the patients. In most of the cases, it started with deterioration of liver function. We did not report or observe any differences between the first and second wave.

Comment 3:

- Have you performed any awake ECMO? What was the neuro status of the non-survivors? Please mention GCS.

Reply 3: Awake ECMO was not performed in any of the patients from our study, although we used it on multiple non-COVID patients in the past. Therefore, the neurostatus and GCS was similar in all patients.

Minor revisions:

Comment 4:

- In the abstract: studies are limited to the first half. Please change it to majority of the studies

Reply 4: It is true that in the meantime different reports appeared and, therefore, we changed this sentence.

Changes in text:

Abstract, Page 2, line 34-35.

Comment 5:

- In the abstract conclusion: add more studies are needed to confirm your signal.

Reply 5:

We added this sentence in the conclusion sentence of the abstract.

Changes in text:

Abstract, Page 2, line 54-55

Comment 6:

- Any role of the staff burnout or limited resources? Can you expand on that aspect?

Reply 6:

This is an important topic which we did not mention. Workload was higher during the second wave, also in our center. We cannot provide data on staff burnout, however, the absolute number of ICU admissions steadily increased and almost doubled compared with that of the first wave in Germany. Even though ECMO materials were barely enough sometimes, we did not experience shortcomings of (ECMO) resources in our center. We added this information, together with literature on the overall ICU situation in Germany in our discussion.

Changes in text:

Discussion, Page 11, line 277-280.

Comment 7:

- Please confirm the percentage of prone position on ECMO

Reply 7:

Yes, every patient received prone positioning before and on ECMO. In some patients, we needed to stop proning during ECMO because of severe complications such as uncontrolled septic shock, or pulmonary bleeding which required bronchoscopy several times daily. We added this information to the discussion.

Changes to manuscript:

Discussion, Page 12, line: 312-313.

Comment 8:

- Table 2: Timing of the lab values Are these lab values before ECMO and at the time of ECMO initiation.

Reply 8:

These values were obtained before the initiation of ECMO. We added this information in the title of the table.

Changes to manuscript:

Table 2: Title

Reviewer F

The authors have analysed the outcomes and characteristics of COVID patients who underwent ECMO comparing the first and the second wave at their institution. While the results reflect what has been happening globally, this would be one of the first manuscripts to bring it out into limelight. However, the authors need to explain the probable reasons for this observation more convincingly and the manuscript needs significant improvement in terms of presentation as well as discussion and conclusion to put things into perspective. I have collated my major and minor comments for the authors' perusal if they wish to make corrections and resubmit.

MAJOR COMMENTS

Comment 1: Abstract:

The conclusion of the abstract sounds more dramatic than befitting their findings. I suggest the authors keep it simple saying that the overall survival rates during the first year of the pandemic was 41%, with a higher number of patients surviving the first wave than the second wave. This corresponded to what has been reported from various live dashboards available from international registries.

Reply 1:

Dear Reviewer F, thank you for the response and we appreciate your comments. Indeed, our conclusion of ECMO outcomes could not be supported by the findings. We adjusted the conclusion into a general statement on all patients and only mentioned that we observed less favorable outcomes in the second wave which is similar to the global trend of various registries. Therefore, we changed the conclusion of the abstract and a

part of the general conclusions.

Changes in text:

Abstract, Page 2, line 52-54.

Comment 2: Introduction:

The opening sentence is a dynamic information and I suggest the authors come up with something generic about the pandemic rather than specific information pertaining to a date.

The introduction should also contain the information on preliminary publications published on planning of ECMO services and the preliminary ELSO guidelines on how ECMO can be helpful in the pandemic. (Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. *Lancet Respir Med.* 2020;8(5):518–26. AND Extracorporeal Life Support Organization Coronavirus Disease 2019 Interim Guidelines: a consensus document from an international group of interdisciplinary extracorporeal membrane oxygenation providers. *ASAIO J.* 2020;66(7):707–21.)

“A study conducted by the Extracorporeal Life Support Organization (ELSO) registry, including 1,035 ECMO supported patients with COVID-19, showed reasonable results with a 90-day mortality of 37.4%”- The study was not conducted by ELSO registry. I suggest rephrase this statement as Analysis of the ELSO registry during the early pandemic showed a mortality of 37.4% in 1035 COVID patients needing ECMO. This should be further supported by the findings of the recently published metanalysis that reported on 1800+ patients needing ECMO till January 2021 which showed a similar mortality. (Extra corporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis. *Crit Care* 25, 211(2021). [https:// doi.org/ 10.1186/s13054-021-03634-1](https://doi.org/10.1186/s13054-021-03634-1))

In September 2020, a second wave of critically ill patients with COVID-19 arose--- The second wave has been variable with regards to timing globally. I suggest authors rephrase this to something along the lines of “The second wave of COVID-19 peaked in Germany after September 2020.....”

Reply 2:

We agree that there was structure- and content-related issues in our introduction. Thank you for the comments, we rewrote the whole section and implemented your comments.

Changes in text:

Introduction, Page 4, line 65-79

Comment 3:

Methods

ECMO settings: Suggest changing the sentence to “Critically ill COVID patients were considered for ECMO based on the following criteria: 1. Those with indications as suggested by ELSO guidelines. 2. Where all other treatment options were exhausted.....”

Reply 3:

We changed the sentence regarding ECMO criteria in our manuscript according to your suggestions.

Changes to manuscript:

Methods, Page 5, line 112-114.

Comment 3.1:

Given that the lab values and ABGs were done more frequently, how did the authors analyse the data statistically for all the 39 patients?

Reply 3.1:

It is right that more variables on lab and ABG were available. Laboratory analyses were routinely performed daily, coagulation parameters were obtained three times daily, and blood gas analyses were performed at intervals of 1–2 h.

We chose the last measurements before ECMO-implantations which were typically in the morning. Then we used the measurement which is at least 24 hours after ECMO-implantation and the last measurement before ECMO-explantation or death.

Statistically, we performed the Friedman’s nonparametric test with Dunn’s correction for repeated measurement because of three time points and two groups. However, we did not display all p-values because it would be too much information in the Figure and difficult to interpret the significant changes over time. We still chose to show the exact lab and ABG values and differences between the groups. We added the statistical information in the methods section.

Changes to manuscript:

Methods, Page 7, line 153-155.

Comment 4. Results:

The results section needs to be trimmed as most of the facts available on the table is duplicated here. The first paragraph looks good. The second paragraph on baseline characteristics should be reduced to include only 5-6 important variables that is statistically significant and is clinically meaningful. (e.g.: median age, RESP scores, MV time and pre ECMO duration of admission in addition to the statistically significant ones.) The readers can pick up the rest of the insignificant results from the table.

Reply 4:

We shortened the paragraph on baseline characteristics. We mentioned the statistically significant differences, and 6 important variables.

Changes in text:

Results, Page 7-8, line 178-191.

Comment 4.1:

Patients of the second wave received less cytokine absorption' if this refers to modalities like cytosorb, I suggest rephrasing this statement.

Reply 4.1:

We rephrased the sentence and called it CytoSorb therapy.

Changes in manuscript:

Results, Page 8, line 187.

Comment 4.2. Outcomes:

This needs to be shortened and part of the outcomes that are non-significant especially the thromboembolic events; pulmonary artery embolism, peripheral venous thrombosis, ECMO-circuit thrombi as well as the breakup of MBE can be referred to Table 3 and Figure 2 than duplicating it in the results section.

Reply 4.2:

We also shortened this paragraph and only mentioned the important variables.

Changes in manuscript:

Results, Page 9, line 226-231.

Comment 5. Discussion: This section is very lengthy and does not convey much information. The authors have highlighted a lot of parameters that could have affected the outcomes, however most of them are non-significant variables from the analysis. I suggest the authors reorganise the discussion section into 4 paragraphs:

1st paragraph: a summary of their findings which is comparable to the results available from EUROELSO and ELSO website but different to what is available on the Japanese ECMOnet as well as similar findings in literature. 2nd paragraph: 3 most important factors that could account for the higher number of deaths during the second wave- late presentation to ICU with concomitant use of steroids and adjuvants, longer ICU to ECMO duration (duration of MV) and higher bleeding. It might be worthwhile looking at the overall ICU mortality in the authors' institution to see if ECMO mortality followed a higher overall ICU mortality. 3rd paragraph: should highlight some of the difference in baseline characteristics as well as the possible higher virulence of the corona virus strain. It also needs to highlight the fact that the second wave had high mortality in most of the countries in Europe including Germany and the phenomenon doesn't confine to patients only on ECMO. Hence despite having some preliminary insights on the pattern of disease as well as on the efficacy of steroids, mortality has been high in critically ill population during the second wave and this was also seen in the ECMO cohort. Likely that ECMO patients were sicker and immunosuppressed (from steroid use, authors' data shows that steroid use increased from 47% to 75%) when it was initiated during the second wave. 4th paragraph: strengths and limitations of the paper.

Reply 5:

Our discussion was very long and did not focus on the relevant topics. We structured it according to the four paragraphs you mentioned. However, bleeding complications have an own paragraph now. This was because we needed to add a high amount of information to this topic. Furthermore, we elaborated some topics (, such as steroid use or need for dialysis) due to the suggestion of other reviewers. These were included in the paragraphs you mentioned.

Changes to manuscript:

Discussion, Page 10-13, line 255-345.

Comment 6:

Did the authors prone the patients on ECMO? A few other centres have tried this during the pandemic with variable results.

Reply 6:

Yes, every patient received prone positioning before and on ECMO. In some patients, we needed to stop proning during ECMO because of severe complications such as uncontrolled septic shock, or pulmonary bleeding which required bronchoscopy several times daily. We added this information to the discussion.

Changes to manuscript:

Discussion, Page 12, line: 312-313.

Comment 7. Conclusion:

single-center study indicates a negative trend of survival rates.

The conclusion segment needs to be rephrased saying that the overall survival in the ECMO cohort was 41% with the number of survivors were higher during the first wave than the second wave, keeping in trend with the higher mortality in the second wave globally. The lessons learnt from their experience can be summarised into a single sentence. The concluding sentence sounds reasonable.

Reply 7:

We adjusted the conclusion into a general statement on all patients and only mentioned that we observed less favorable outcomes in the second wave which is similar to the global trend of various registries.

Changes to manuscript:

Conclusion, Page 13, line 362-365.

MINOR COMMENTS

The minor comments confine mainly to grammar errors. I have highlighted a few, but I suggest that the authors look more closely at this before submission.

Comment 8:

‘for such cases, the use of extracorporeal membrane oxygenation (ECMO) therapy can be considered’ - suggest rephrasing it to ECMO is indicated in severe ARDS and its use during COVID pandemic has been reported globally.

Thus, there is a need for new analysis of ECMO therapy data, including admissions of patients- There is limited literature on the outcomes of ECMO during the second pandemic wave and hence further analysis of ECMO therapy data during this period is warranted.

Reply 8:

We corrected both sentences in the introduction.

Changes in manuscript:

Introduction, Page 4, line 71-72.

Comment 9:

‘Patients had received numerous other therapies before employing ECMO, with high frequencies of iNO inhalation, NMB agents, antibiotics, and corticosteroids.’ – Suggest rephrasing it as ‘Most of our patients received, NMBA, Antibiotics, steroids and iNO prior to initiation of ECMO.’

Reply 9:

We corrected this sentence in the discussion.

Changes in manuscript:

Discussion, Page 9, line 235-236.

Comment 10:

‘However, outcomes of ECMO therapy in the second wave of the COVID-19 pandemic were not as successful as those obtained during the first wave in terms of survival; these rates were similar to those recorded in other centers using ECMO’- suggest rephrasing this as ‘However, the number of ECMO non-survivors were higher during the second wave, in line with the higher mortality reported during the second wave globally. Similar trends were observed in other centres using ECMO during the second wave, irrespective of the burden of the pandemic.’

Reply 10:

We corrected this sentence in the discussion.

Changes in manuscript:

Discussion, Page, line 238-241.

Comment 11

Raasveld et al. reported that non-surviving patients were more acidic prior to the initiation of ECMO- suggest rephrasing this as Raasveld et al. reported that non-survivors were more acidotic prior to the initiation of ECMO

Reply 11:

We rephrased this sentence in the discussion.

Changes in manuscript:

Discussion, Page 13, line 324-326.

Comment 12:

During the second epidemic wave, outcomes deteriorated and we reported higher mortality and significantly more bleeding events. -- During the second pandemic wave, we reported significantly more bleeding events and a higher number of non survivors.

Reply 12:

We corrected this sentence in the discussion. It is the introduction of the paragraph on bleeding complications.

Changes in manuscript:

Discussion, Page 11, line 281-282.

Reviewer G

Summary:

This article is a single center retrospective chart review on an important topic; the use of ECMO in COVID ARDS patients. It directs its attention to the differing outcomes (mortality, bleeding) between the first and second wave, as well as differing treatment strategies and laboratory parameters.

The authors note previously published literature suggests worsening survival in COVID ARDS treated with ECMO during the second wave. The authors saw a similar trend but did not achieve statistical significance. Patients from the first wave were statistically more likely to have higher BMI, higher PEEP, and more incidence of pre-ECMO pulmonary HTN. Among other items, patients from the second wave were statistically more likely to have a major bleeding event, and had a higher pH on ECMO initiation. The proposed contributing factor to the possible increase in mortality cited by the

investigators include late presentation to ECMO capable centers and difficulties in communication with referring institutions. The authors note that while the incidence of major bleeding events increased, there was no difference in the amount of blood products administered. They also note the role of new viral strains is unclear.

Suggestion: Accept with Major Revisions

Major Comments:

Comment 1:

This paper presents a large body of data regarding an important group of patients who require further study, however the discussion requires significant revision.

The authors note a reported increase in mortality in the second wave in the literature, and a similar trend towards this in their data set. The data does not support statistical significance in this finding. As such, they cannot support that there was a difference between the first and second wave of patients in this respect. The primary possible contributing factor the authors cite is late referral from other hospitals, thus extending the pre-ECMO mechanical ventilation time. However, there is not much additional analysis given on this point regarding which patients those were who had been referred late, and if they differed from the rest of the cohort. This could be an important area to investigate and could be the focus of the discussion. As written, the data does not support several sections of the discussion

Reply 1:

Dear Reviewer G, thank you for the response and we appreciate your comments.

Indeed, our data does not support that the mortality was significantly higher in the second wave. Therefore, we changed our conclusion to a general statement on the overall mortality and that we observed less favorable outcomes which were similar to various registries. Furthermore, we rewrote the whole discussion. It starts with our findings, and we clearly mentioned that the mortality difference is not statistically significant, however, clinically relevant because other registries showed a similar negative trend, and they were statistically significant due to more patients.

Referring to your next point, the late presentation of possible ECMO candidates, we wrote a separate paragraph. We performed separate statistical analysis on pre-ECMO ventilation time, however, it did not reveal any significant results. Nevertheless, we discussed our descriptive analysis (Table 1 and 3) because it showed long periods of

ventilation which exceeded limits of current guidelines. We discussed current guidelines and added insights from other studies about this topic.

Changes in manuscript:

Discussion, Page 10-11, line 242-280.

Conclusion, Page 13, line 362-365.

Comment 2:

Patients in the first wave had statistically significant higher PEEPs and incidence of pulmonary HTN while patients in the second wave had a statistically higher pH. While there was no difference in P/F ratios between the two groups, this suggests the possibility of more severe ARDS in first wave patients. It is interesting therefore that there was a trend towards mortality in the second wave when the patients appear to have been “less sick”. There is some concern that there was variation in patient selection that led to these differences. The protocol for patient selection for ECMO in this institution should be discussed. Similarly, the variation in patient selection between the two waves should also be discussed.

Reply 2:

Our selection procedure of ARDS patients for ECMO was conducted according to the ELSO guidelines and, during the study period, we did not change our protocol for ARDS patients as we reported positive results during the first wave. We added information in variation of patient selection, as example, we found more patients who already received steroids. Indeed, pH and PEEP values indicated more severe illness in first wave patients. We discussed these dubious findings and have some possible explanations. Acidosis in ARDS patients could be due to a therapeutic modality, which is known to have a protective effect against ventilator-associated lung injury. And low PEEP adjustments could indicate less lung compliance, which is associated with mortality in patients with ARDS on ECMO. We changed the whole section and answered all your comments.

Changes in manuscript:

Discussion, Page 12-13, line 310-345.

Comment 3:

The authors also note an increased risk of bleeding, but no change in either

anticoagulation strategies or blood product administration between the two groups. This finding should be expanded on.

Reply 3:

We discussed bleeding complications and possible reasons. Furthermore, we think that interpretation of differences in PRBC units is difficult because the classification of major bleedings established by the ISTH is excessively stringent. Besides that, PRBCs are administered frequently to maintain appropriate Do₂:Vo₂ ratios and hemoglobin levels. As a result, PRBC units for incidental bleedings cannot stand out in a statistical comparison. We mentioned more details on this issue and other topics in the revised section.

Changes in manuscript:

Discussion, Page 11-12, line 281-309.

Comment 4:

An interesting theme that was not mentioned was how COVID patients were overall managed in the first wave vs the second wave. While this may not be generalizable to all centers, in this writer's region significantly less non-invasive ventilation was used due to the concern for the safety of healthcare staff. By the second wave, non-invasive was used broadly. What impact, if any, this has on patient selection for ECMO and ECMO survival is unclear.

Reply 4:

In Germany, there were multiple important differences between the first and second wave regarding overall management of COVID-19 patients. We discussed outcomes, ventilation, and treatment differences in a separate section.

Changes in manuscript:

Discussion, Page 9-10, line 255-280.

Comment 5:

Finally, the authors briefly note in their discussion and conclusion that the role of shifting viral mutations on patient course and ECMO outcomes is unclear. While this is certainly true, they do not provide much additional review and it distracts from some of the findings of the paper. I would omit this as this is not part of the data.

Reply 5:

We also think that it should be omitted, as we did not investigate this topic. We removed it from the discussion.

Minor Comments/Line revisions:

Comment 6:

Line 170 – Would be interesting if they commented on other medical therapies. By September I think tocilizumab was out of favor. Was this used in that region?

Reply 6:

Yes, we started using tocilizumab when the results of REMAP-CAP and RECOVERY investigations became apparent. Currently, after discussing this in the German guideline committee, we would not use it in patients on ECMO.

Comment 7:

Line 254 and subsequent paragraph – Interesting points raised here regarding potential poor prognostic signs for ECMO. The authors note many of the patients in their study exceeded the MV limit. Could this explain some of the trend towards worse mortality they appreciated? Would be helpful if authors expanded here

Reply 7:

We think this was an important factor and it was also an observation from the data of the ECMOnet registry. The database of the ELSO registry did not allow for adjustment of time from mechanical ventilation to ECMO, but Broman et al. mentioned it as a possible factor in the correspondence. Therefore, we expanded on this issue in the discussion.

Changes in manuscript:

Discussion, Page 10-11, line 255-280.

Comment 8:

Line 308 – As this is one of their significant findings it would have been nice to delve more in here

Reply 8:

This was an interesting finding. Reasons for platelet decrease during ECMO therapy are frequently seen and the underlying cause is multifactorial. Another important factor for lower platelet levels before explantation of ECMO in patients of the second wave

is that ECMO runs were longer, too (16 vs. 24.5 days, $P = .074$). We discussed this issue in more detail and added it to the section on bleeding complications.

Changes in manuscript:

Discussion, Page 10-11, line 281-309.

Reviewer H

This is a retrospect review of ECMO that was performed on patients with COVID-19. The authors report a total of 39 patients with ECMO whose median age was 56 years ago. The majority of them being males. The reports are results of mechanical ventilation prior to ECMO placement as well as the overall survival of 41%.

Comment:

The authors note that a number of the studies that were presented represented the first half of 2020. It is true; however, that a number of other reports have come out since that time that report results for a further longer period than simply that period.

Reply:

Dear Reviewer H, thank you for the response and we appreciate your comments. It is certainly true that data from multiple registries showed a negative trend, even with statistical significance (ELSO). Therefore, we updated the background sentence of our abstract and discussed multiple reports which dealt with this topic and were released in the last weeks/months.

Changes in manuscript:

Abstract, Page 2, line 34-35.

Discussion, Page 10, line 242-254.