Peer Review File
Article information: https://dx.doi.org/10.21037/aob-21-82

Overall Response:

Thanks for taking out time for timely reviewing the article and giving us your useful feedback. We liked the way reviewers have been selected by the journal; one focusing more on the clinical side of the review while other more on the research aspect. This makes it a well-rounded review to be looked upon.

We initially submitted our report in 2021 with addition of published data prior to July 2021. There have been delays in the process due to multiple reason, which lead us to review it in early 2023. According to PubMed (https://pubmed.ncbi.nlm.nih.gov), In last 2 year, 6101 articles have been published on extracorporeal life support, generally [Syntax: (((ECLS) OR (ECMO)) OR (extracorporeal membrane oxygenation)) OR (Extracorporeal life support) AND (2021:2022[pdat])]. This is the highest number of articles published in any two-year period on this topic. We think that stating *"lack of data or literature"* by just focusing the data until July 2021, without reviewing the new available evidence would not be helpful or justified. The availability of a large data with new evidence in this field between our initial submission (2021) & this review (2023) was the main reason that we had to rewrite and restructure it almost entirely. For this reason, we expanded our team by adding 2 more authors; Dr. Muhammad Abd Ur Rehman and Dr. Hina Akram.

In this review you will find following changes, generally:

1- The data covered will be up to December 2022.
2- Most of the references are directly ECMO-related (69/90), while rest of those (21/90) are given while stating the topic in general or while comparing an ECMO with non-ECMO study.
3- Summary of the evidence available on a specific topic is tabulated separately in each narrated part. I will make easier for the reader to follow.
4- Studies are documented in the chronological order in the tables while in the text, it is there as per the discussion.
5- The discussion on specific blood product is well-structed now, starting form general introduction of the product, followed by its indication and recommended dosing schedule in ECMO and lastly, it's morbidity & mortality benefits if available.

Moreover, we emailed 55 professionals of reputed ECMO institutes, asking then about any institutional guidelines available for non-PRBC blood product transfusion. 15 of them replied and none of them stated following any specific local or institutional guidelines as mentioned in our original article. We have removed this in the revised version due to following reasons:

1- Very poor response (27%) from the ECMO professionals being emailed.
2- This information is not adding anything other than what is already known i.e., lack of institutional guidelines and widespread difference in practices of blood product transfusion protocols (1,2).

3- Despite the difference in the blood product transfusion protocols, some protocols are being followed by different ECMO centers (e.g., https://links.lww.com/ASAIO/A628). So, professional's reply of "no protocol is being followed" doesn't go with the general evidence. (1-3) We believe a poor response rate is the cause of this unexpected reply.
4- This information is more than 18 months old, and a lot of new evidence is available after that, which is discussed in detail in the revised version.

Reviewer A

Comment 1: *"Some of the products were reviewed in detail and others more cursorily, without a clear structure to the reviews"*
Reply 1: The main reason of inconsistency in the detail of different topics discussed is the inconsistency in the data available. In the revised version we have outlined the data available and used for the review in table 2. Additionally, in the review you will find it a well-structured now as mentioned above.

Comment 2: *"Some of the references are for ECMO specifically and others for critically ill patients in general."*
Reply 2: In the revised version, we have tried to use almost all references related to ECMO patients, however, wherever there are non-ECMO references, we have mentioned that clearly in the text. (e.g., line 171-173, 207-208, 239-241, 281-283, and 298-302 in the revised version)

Comment 3: *Title: "other than" would read better than "different from".*
Reply 3: We agree with that & is changed.

Comment 4: *"Abstract is generally fine other than the "Discussion"; this is a sort of summary of data points but somewhat random (no transfusion threshold for platelets but for others)"*
Reply 4: We agree & we have rewritten and made it more structured.

Comment 5: *"Line 23 The second half of the sentence is oddly phrased and nonspecific: obviously shorter time on ECMO is better, but are there specific recommendations to shorten the duration?"*
Reply 5: We couldn't find a specific guideline to "shorten the duration on ECMO", so we have removed that part in line 38-39 of the revised version.

Comment 6: *"Introduction: Generally concise and well written. Would typically define ECMO, both the abbreviation and also the basic process."*
Reply 6: ECMO is defined as well as explained in line 56-60 of the revised version.

Comment 7: *"Line 45: bleeding is not typically the most common cause of mortality (lack of recovery is much more common) better described as the most common lethal complication of ECMO therapy."*
Reply: Agreed and changes made in line 74-75 of the revised version.

Comment 8: *"Line 51: reference 7 is about platelets, mostly neonates and does not support this sentence"*
Reply 8: Agreed. Appropriate reference given in the revised version in Line, 80, Reference 8 (4).

Comment 9: *"Line 58: would reference this checklist"*
Reply 9: Done. Reference number 92.

Comment 10: *"Line 66: how many people replied to these emails? Hard to believe not a single institution had guidelines/protocols?"*
Reply 10: As mentioned above, 15 out of 55 replied to the email. None confirmed following any specific protocol. Some institutes where anticoagulation & transfusion guidelines (https://links.lww.com/ASAIO/A628) are being followed (4) showing reduction in complications (Reference 16 in the revised version). Due to these reasons, this part is omitted from the revised version.

Comment 11: *"Discussion: As above would begin with a general discussion about what information is available in this area; randomized trials, retrospective work, etc."*
Reply 11: Revised (111-128)

Comment 12: *"Lines 70-77: Please specify if these are about PRBC transfusion or other product transfusion. Detail what are the effect on outcomes for other products."*
Reply 12: This is just the start of discussion (Line 111-124 in the revised version), where we are discussing blood products in general (including PRBC as well as non-PRBC blood products). Effect on outcome of other products has been discussed in the individual sub-headings in the following discussion. We believe it was already clear in the initial manuscript, but we have made it clearer in the revised version (Line 117).

Comment 13: *"Please state whether there is any work comparing priming techniques and outcomes. This simply lists options."*
Reply 13: There are multiple studies comparing different priming techniques (5-7), but we believe, mentioning those in the article will drag us away from the actual discussion on non-PRBC blood product transfusion. We have rephrased the priming part in the revised version (line 130-147) to make it more streamlined with the discussion but still don't believe the addition of information asked by the reviewer will benefit the reader much, in context of our original topic.

Comment 14: *"Product specific sections: These would be much improved by a consistent structure used for each section. Would suggestion these questions: 1. Why is the product needed on ECMO (this is paragraph 2 of platelets but not explicity stated for FFP/cryo), 2. what are the consequence positive and negative of transfusion 3.what are common practices 4. what is the evidence for these practices—what is and what is not available"*
Reply 14: The discussion on specific blood product is well-structed now, starting form general introduction of the product, followed by its indication and recommended dosing schedule in

ECMO and lastly, it's morbidity & mortality benefits if available. You will find an evidence-based discission in its entirety.

Comment 15: *"would move paragraph 2 up as above"*
Reply 15: This portion has been rephrased, rearranged and re-written (149-165).

Comment 16: *"Line 98-107: This guideline specifically does not have recommendations for ECMO and the PLT and FFP guidelines are not necessarily based on ECMO patients, (Vlaar): should mention that specifically or just remove, likely does not add anything"*
Reply 16: In the revised version, we have mentioned it clearly that this not a recommendation for ECMO patients (Line 171-173), but we still want to keep it as it still covers critically ill patients and gives us an idea about the thresholds that can be studied in future on ECMO patients as well.

Comment 17:" Line *113: the use of antiplatelet?"*
Reply 17: Yes, reference 10 in the revised version. (8)

Comment 18: *Line 121: "would specifically discuss what side effects"*
Reply 18: Stated in the revised version (Line 201-204)

Comment 19: *"Line 127: ref 27-29 are these ECMO patients? If not would remove"*
Reply 19: These references (36-38 in the revised version) are not EMO patients (mentioned clearly in the revised version in Line 207-208), however, we would like to keep these references as our further discussion on ECMO patients as built on it.

Comment 20: *"Final paragraph: this is a reasonable summary of FFP but would state whether or not these would ECMO patients"*
Reply 20: These are critically ill patients including the ones on ECMO support. As mentioned by the author in original study "We planned to extract data on co-interventions (i.e., transfusion of red blood cells and platelets, fibrinogen or other specific coagula- tion factors, steroids, need for surgery and **need for extracorporeal life support**) related to the main outcome." (9) We have also mentioned it clearly in the revised version (Line 239-241).

Comment 21: *"This reference should be included: Evaluation of effect of scheduled fresh frozen plasma on ECMO circuit life: A randomized pilot trial. McMichael ABV, Zimmerman KO, Kumar KR, Ozment CP."*
Reply 21: Thanks for pointing it out. Added in Line 227-231 (Reference 41) of the revised version.

Comment 22: *"There is information on albumin (molecular weight, etc) which is not included for other products and likely unnecessary"*
Reply 22: Removed (294) from the revised version.

Comment 23: *"Lines 170-171 would move to priming section"*
Reply 23: Moved.

Comment 24: *"The addition of the discussion of the viscoelastic testing/TEG seems to not fit with the other objectives of this paper, there is no discussion of other coagulation testing, indeed that would be a separate work. It is conceivable that TEG directed transfusion of non-PRBC blood products could be helpful in ECMO; that is typically how TEG is used: but the references seems to mostly be from non-ECMO TEG papers with one exception and do not fully support the implications of the abstract."*
Reply 24: We have added this part as it is of prime importance in following the coagulation status of the patients on ECMO support and we believe that this part will help the readers understand more about the quick means to get the coagulation status of the patients on ECMO. That's why we want to keep it. However, the references are updated in the revised version.

Comment 25: *"The figure provided is potentially useful but needs more context. When was this implemented at the institution. How many patients has it been trialed on. What is the data on blood product usage, hemorrhagic and thrombotic complications? Is there enough for a paper."*
Reply 25: This flowsheet is showing our institutional practice to manage hemorrhagic episodes on ECMO in medical intensive care unit in Hamad General Hospital (HGH). It is based upon recommendations in the ELSO Red Book, expert opinion at HGH, and published literature referenced in this review. This is not trialed, and clinicians at our institution use it as an aid; however, it is not a mandatory guideline that is followed.

Further comments:

Comment 1: *"The phrase 'multiple original articles' in line 102 is redundant and doesn't need to be included in the list of types of articles searched."*
Response 1: Agreed.
Changes in the Text: Removed as requested in the edited version.

Comment 2: *"Currently, there is no "Results" section and the "Discussion" section is mostly describing the results of the literature search. Tables 3-8 should be incorporated into a separate Results section……"*
Response 2: Agreed.
Changes in the Text: A result section has been added separately with relevant tables.
Another column is added in all the tables to their left commenting on the GRADE *(Grading of Recommendations, Assessment, Development, and Evaluations)* quality of evidence. This grading is done based on the assessment of each study. As recommended, text accompanying the tables regarding the type of studies reviewed has also been included in the results section.

Comment 3: *"Your discussion section should begin with an overview of your findings that there is limited evidence underlying current ELSO recommendations. This opening paragraph……."*
Response 3: Agreed.
Changes in the Text: Discussing section has been restructured to make it more homogenous.

Other changes in the text: The summary section has been restructed to include the literature gap and future research needed to improve the body of evidence guiding transfusion.

Other changes in the text: *Both of the articles provided in the previous reviewer comments have been added to the amended text accordingly.*

Reviewer B

From the respected reviewer B's overall comments, we could assess that the reviewer needs explanation/ changes in the text regarding following 6 points:

1. *The literature search strategy and the literature included for the review.*

There had been some ambiguities in the original manuscript regarding the literature review which has been taken care of in the revised version. The detailed literature search strategy has also been explained in the methodology section.

2. *Needs more explanation of 55 professionals contacted for their institutional non-PRBC blood product transfusion protocols.*

As we have explained earlier, 15 out of 55 replied to the email. None confirmed following any specific protocol. However, we have omitted this section in the revised version due to the reasons mentioned above in the *"Overall Response"* section.

3. *Doesn't seem happy with repeated referencing of 5th edition of ELSO Red Book.*

As it is evident by the review that the available literature is not enough for definitive guidance on this topic, that's why we have to rely on one of the most trusted authoritative texts in this field i.e., ELSO Red Book, written by more that 200 experts in the field. (10) The lack of literature of high-grade evidence is the main reason of reliance on the book. However, we have minimized the Red Book references as much as possible in the revised version.

4. *Wants the strengths of recommendations mentioned in the text.*

It's mentioned clearly in the Summary section.

5. *Suggested 2 studies to be included in the review.*

Northrop, et al.'s study (11) has been mentioned in the revised manuscript in the section of TEG/ROTEM (Reference 87). But, the other study (12) didn't appear in our search, according to our search strategy mentioned above. However, we read the article mentioned by the reviewer. It is related to comprehensive, context-responsive anticoagulation and transfusion guideline on bleeding and thrombotic complication rates and blood product utilization during ECMO where there was no statistically significant difference observed in non-PRBC blood product transfusion. We opted not to include it in the revised version due to following reasons:

a) there was no statistically significant difference observed in transfusion of the products being reviewed in the article.
b) Reason (a) might not be enough to exclude it, but we decided to stick to our original search strategy, to make it more streamlined & search to be reproducible.

6. Expecting references to be approaching 100.

At the time of submission of original article, 2021, there weren't enough data to be included but now, we have gathered enough references more systematically and included in the study.