

Peer Review File

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Reviewer A

The authors are to be commended on this well designed, single center study that is relatively novel in examining the impact of VV EVMO on acquired vWS within a narrow niche of single lung transplant recipients. The major limitation of the study is the small size and this leads to major criticisms of the study detailed below. While not prohibiting in acceptance for publication, it is the opinion of this reviewer that the manuscript needs to be revised in its conclusions.

Major criticisms:

Comment 1: This is a relatively small study. This cannot be helped other than waiting long to accrue a larger number of patients. However, it should be mention in the conclusion that given the findings of the present study, a larger study is indicated in order to determine the impact of VV ECMO on bleeding and transfusion requirements. I would hypothesize that in fact acquired vWS associate with VV ECMO is in fact associated with increased transfusion requirements and more PGD. The present study is too small to test this hypothesis, but one of the major implication of this study is to mandate a larger study to test whether acquired vWS seen with VV EVMo is associated with worse outcomes such as increased transfusion requirements and increased PGD.

Reply:

We appreciate the reviewer's positive feedback. Especially, the comment 'I would hypothesize that in fact acquired vWS associate with VV ECMO is in fact associated with increased transfusion requirements and more PGD' strongly encourages us.

Changes:

We have added some comments on the future larger larger-scale study in the discussion (see Page 15, line 319-322) and the conclusions (see Page 15-16, line 336-338).

Comment 2: The authors should discuss the criteria involved in the determination as to whether VV ECMO should be used versus no ECLS. Presumably VV ECMO was used when the patient could not tolerate single lung ventilation. Was this decision made pre-operatively or did some lung transplants start without VV ECMO and then convert to VV

ECMO intra-operatively? Exactly what criteria were used?

Reply:

We appreciate the comments. We completely agree that we should clearly show the criteria for ECLS in the manuscript.

Changes:

We have made changes in the method (see Page 7-8, line 156-165).

Comment 3: In the discussion, the authors state:

However, the vWF large multimer index was maintained at > 75% in average at the end of SLT in the ECMO group, which did not significantly affect the intra- and postoperative outcomes including blood loss, blood transfusion, and re-exploration thoracotomy for bleeding.

Additional discussion about the small size of the study is warranted here. As noted above, the sample size may simply be too small to demonstrate a difference between the two groups with respect to bleeding, transfusion requirements, and PGD. I believe this is a type II statistical error, and while this is unavoidable, it should be discussed. The authors could use a power calculation to determine the necessary study population to demonstrate, for instance, and statistically significant 20% increase in blood transfusion or PGD with VV ECMO, just to give an example.

Although this is mentioned briefly mentioned at the end of the manuscript (lines 301-303), it should be addressed sooner and in more depth.

Reply:

We sincerely appreciate the reviewer's comments, particularly the idea that 'the sample size may be insufficient to demonstrate a significant difference between the two groups,' by which we were encouraged. We are planning a nationwide study of von Willebrand factor large multimers during lung transplantation. We have added our thoughts on these points in the discussion as well as in the conclusion.

Changes:

We have made some changes in the discussion (see Page 13, line 285-288; Page 15, line 319-324) and the conclusion (see Page 15-16, line 336-338).

Comment 4: Related to the comments above, I do not think you can make this conclusion. You can only say that the present study was not sufficiently powered to determine the impact of VV ECMO on bleeding, transfusion requirements and PGD. I do not think that you can conclude that the impact on bleeding complications was limited as you say here: However, the vWF large multimer index in the present study remained at an average of > 75% and was as low as 30–40% at the end of surgery with VV ECMO, and its impact on bleeding complications was limited.

Reply:

We thank the reviewer's comments. Now we understand that 'its impact on bleeding complications was limited' should not be included into the conclusion.

Changes:

We have made some changes in the conclusions (see Page 15, line 334-336).

Minor criticisms:

Comment 5: This sentence sounds awkward.

"Among ECLSs, cardiopulmonary bypass (CPB) had been reported to increase blood transfusion due to coagulopathy and inflammatory response [5]. "

When writing consider how a sentence sounds when the reader hears the text in their head. The phrase "Among ECLSs" would never be used in spoken English because the of the juxtaposed "Ss" which cannot be easily pronounced. I would try some like, "Among different types of ECLS, cardiopulmonary bypass (CPB) had been reported to increase blood transfusion due to coagulopathy and inflammatory response".

Reply:

We appreciate the reviewer's comment. We have adopted the suggestion.

Changes:

We have made a change in the introduction (see Page 5, line 102-103).

Comment 6: The amount of time on VV ECMO on single lung transplant seems longer than one would expect. Can the authors compare this to other studies that report outcomes of lung transplant using VV ECMO and discuss why this might be different? Is it because patients must be cannulated before positioning and prepping and draping? Then

decannulated after the chest is closed and the patient is placed supine?

mean intraoperative ECMO time in the ECMO group was 487 ± 14 (443 – 557) minutes

Reply:

We thank the reviewer for the comment. As the reviewer expected, we initiated VV ECMO support immediately after the induction of general anesthesia (before the start of the surgery). Weaning from VV ECMO support was attempted upon completion of the surgery. We explained this in the methods.

Changes:

We have made changes in the methods (see Page 8, line 167-179).

Comment 7: I know what the authors are trying to convey here, and we all use terms like "oozing" in our common vernacular, but this language is not suitable in a formal, peer-reviewed scientific journal. It also refers to a subjective finding with no objective clinical relevance as the authors admit. This sentence should be omitted, in my opinion.

2 of the 5 patients had massive bleeding events, while the oozing type of bleeding at the skin of the sites of cannula insertion was observed in all 5 patients, indicating an apparent hemostatic disorder [10].

Reply:

We appreciate the comment. We rephrased the sentence.

Changes:

We have made a change in the discussion (see Page 14, line 300-302).

Reviewer B

Comment 1: The study was deemed as a prospective one in the Introduction section, and as a retrospective study in your IRB statement. Please confirm which one is correct and which checklist is more suitable for your article at the same time.

Reply: I found that the comment in the statement was not correct. This is a 'prospective' study that is registered to the UMIN Clinical Trials Registry (UMIN-CTR), UMIN000018135 (https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000019166). I have also confirmed that the checklist (TREND checklist) is suitable for this study.

Comment 2: LT/CB/Ag should be defined upon first use in the Main Text.

Reply: “LT,” is defined on page 12, line 264. “
CB” is defined on page 15, line 316.
“Ag” is defined on page 9, line 194.

Comment 3: “Large-volume transfusions of red blood cells (RBCs) and platelets have been reported to be associated with various complications in lung transplant recipients in multiple studies [1].” Studies were mentioned, but only one reference was cited. Please confirm whether more references are needed.

Reply: I added more references for the sentence.

Comment 4: “The data are represented as a box and whiskers plot.” The above sentence was suggested to be replaced with “The data represented a box and whiskers plot.” Please confirm whether the indicated meaning remains correct.

Reply: I confirmed that the indicated meaning remains correct. I replaced the sentences in the main text as well as in the figure legend.

Comment 5: Figure 3

*”immediatly” - please review the word.

*Definition of NS should be defined.

Reply: I corrected the spelling of “immediatly”. “NS” is defined on page 22, line 457.

Comment 6: Figure 4

*Definition of NS should be defined.

*Asterisk in the figure should be explained in the legend.

Reply: “NS” is defined on page 22, line 473. * (Asterisk) is defined on page 23, line 23.

Comment 7: Table 1

*COPD is not completely defined in the explanatory legend.

*A header is required in the first column.

Reply: I defined “COPD” completely in Table 1. I added a header in the first column in Table 1.

Comment 8: Table 2

*Should the case number start at No. 1 and follow with subsequent numbers?

*There is no abbreviation for “Pleural adhesion grade”. Please confirm whether it can be removed from the explanatory legend.

Reply: I put No.1 in the case in the first line and subsequent numbers in the following lines as your recommendation. I need to remain the explanatory legend for “Pleural adhesion grade”.

Comment 9: Table 3

*There is no C marked in the table. Please confirm whether it should be added or the explanation added in the explanatory legend should be removed.

*A header is required in the first column.

Reply: I added an explanatory legend for the 90-day mortality in the ECMO group. I added a header in the first column in Table 3.