Peer Review File

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Reviewer A

Comment 1: In the introductory paragraph are the authors proposing a VA ECMO approach for all LTx procedures, or only where MCS is required? If the latter, this should be clarified. If the former, then the authors should soften the introduction to reflect the data supporting the benefits of off-pump transplant where MCS is not required.

Response 1:
The latter is correct – we support a VA ECMO in case MCS is required during the lung transplantation procedure. According to the reviewer's suggestion, this is clarified in Introduction as well as through the text in a revised version.

Comment 2: This is a very well written manuscript, but I am a little confused by the structure. Is it a brief correspondence, editorial on another paper or review? In parts there are statements made without supporting data, is this published somewhere else? For example, sentence starting page 4, line 125 – "differences were smaller than expected" – is there data somewhere to support this statement? There are more statements like this throughout the manuscript which would benefit from supporting data. I think the information conveyed in this manuscript is very important, perhaps it would be better structured as a conventional article with methods/results?

Response 2:
This is a short review/editorial, not on another paper but on a specific idea with peripheral VA-ECMO in the context of lung transplantation where the original supporting data at a high-volume transplant center are also presented. Those data were not reported anywhere before but are presented through this review for the first time to share the key points with the readers of JTD. Although two large data sets are from the different cohort of the patients, while both of them are so unique that they help the readers better understand the central messages through the relevance of peripheral VA-ECMO approach in a concerted manner, this is reported in the current form rather than a standard clinical research manuscript.
Regarding a question about the data described in page 4, line 125, yes, they are revised in the main text as well as presented in Table 3 in order to clear the question from the reviewer.

Comment 3: Do the authors plan to publish their data on the impact of calcification scores in another format, if not, inclusion of more granular data would be beneficial, including whether candidates were denied candidacy at the centre based on the presence of high calcification scores. Additionally, the authors should consider including the 30-day and 1-year survival percentages for those with low and high calcification scores, PAD, AAA.

Response 3:

According to the reviewer's suggestion, in addition to the revision as stated above in Response 2, we have added the data of 1- and 3-year survival in both groups and comments as follows: The 1-year survival was remarkably worse in the high score group than in the low score group, however, survival conditional on hospital survivor appears to be comparable between the two groups

Comment 4: Page 4, Line 122 – did the 3 patients with severe PAD, undergo transplant with central cannulation or were they excluded for transplant? Sentence needs clarification.

Response 4:
Yes, all of those three patients underwent lung transplantation with VA-ECMO using central cannulation to avoid peripheral cannulation-associated complication risks. According to the reviewers' advice, we clarified the statements in the main text in a revised version.

Reviewer B

In this preliminary study, the authors have assessed the safety and risk of the lung transplant procedure using peripheral VA-ECMO. I have some comments as follows.

Comment 1: In this study, 78 patients underwent lung transplantation using peripheral VA-ECMO. All the patients were peripherally cannulated for minimally invasive transplant through antero-lateral thoracotomy? Please clarify the indications of peripheral VA-ECMO.

Response 1:
Yes, we confirm that all 78 patients underwent lung transplantation through antero-lateral thoracotomy approach with peripheral VA ECMO as intraoperative MCS. Antero-lateral thoracotomy approach is our standard approach for all lung transplantation cases while we haven't used clamshell approach for any complicated cases for the past years. According to the reviewer's suggestions, we clarified them through the main text.

Comment 2: The authors assessed PAD by CT scan in all lung transplant candidates over 65 years of age. Why did they assess PAD score in 130 lung transplant patients over 70 years of age, not 65 years of age?

Response 2:
Due to the insurance coverage, currently CTAP for PAD assessment is available only for those aged above 65. While there has been a steadily increase in the number of lung transplant recipients who are older than 70 years of age, in aging population, many patients have multiple diseases characterized by acceleration of the normal aging process, such as cardiovascular disease including PAD. Our preliminary data also supported the correlation between PAD and suboptimal transplant outcomes among the elderly patients, as a part of the programmatic project with geriatric lung transplantation. Given together, we focused on those aged above 70 with PAD as high-risk group.

Comment 3: Do the authors consider that the minimally invasive lung transplant procedure with peripheral VA-ECMO can be employed as a standard procedure for all the patients or just elderly patients? Please discuss about that.

Response 3:
Yes, the minimally invasive lung transplant procedure with peripheral VA-ECMO approach can be applied for all the patients as a standard procedure as it is currently at our center while the pitfalls as well as inherent limitations need to be appropriately understood, which is our central message through this review. We duly revise the text accordingly.

Reviewer C

Comment 1: I believe this manuscript should be reformatted and resubmitted as an original article.
In my opinion does not fit the journal description of an editorial.

Response 1:
Thank you for the comments. This is a short review/editorial, not on another paper but on a specific idea with peripheral VA-ECMO in the context of lung transplantation where the original supporting data at a high-volume transplant center are also presented. Those data were not reported anywhere before but are presented through this review for the first time to share the key points with the readers of JTD. Although two large data sets are from the different cohort of the patients, while both of them are so unique that they help the readers better understand the central messages through the relevance of peripheral VA-ECMO approach in a concerted manner, this is reported in the current form rather than a standard clinical research manuscript.

Reviewer D

Comment 1: The authors have made a concerted effort to highlight and share their experience of successfully utilizing a peripheral VA ECMO approach during lung transplantation. They also provide insights into the risk stratification process of using calcification score as a differentiating predictor of complications post-lung transplant.
However, the report lacks essential details to make meaningful conclusions.
1. Operative details, including ischemic times, need/reasons to convert any of the patients from peripheral to central VA ECMO
2. Post-operative outcomes including PGD/ICU and hospital LOS
3. Long-term outcomes (if available), especially survival in patients with low vs high calcification score

Response 1:
Since this is a short review/editorial, given the limited number of the tables and figures as well as words limits, we included the limited but key data which are in line with the points delineated in the text. According to the reviewer's suggestion, we have added the data of long-term outcomes for both groups of

low and high calcification score in a revised version.

Comment 2: With regard to differential hypoxia and its duration and severity, the authors report
'It should be noted, however, that no serious neurological consequences resulted from the incidents of differential hypoxemia, and all the patients, including those with severe differential hypoxemia during transplant, were discharged from hospital uneventfully following lung transplant'
Hypoxia-induced brain injury can induce a wide spectrum of neurological deficits ranging from mild cognitive/attention deficits to severe neurologic damage. Reassuringly, the report suggests that there were no devastating neurologic insults. It is imperative for the audience to learn if the patients were assessed for more subtle forms of hypoxic neurologic insults.
Beyond these concerns, I think adding a comparative historical or contemporaneous cohort of patients with alternate intra-op MCS strategies for lung transplant would add more weight to the study.

Response 2: Thank you for your valuable suggestions.
Yes, we confirmed that all the patients cleared even a small concern about possible hypoxic neurologic insults on clinical exams and additional testing if indicated including Head CT and/or MRI.
In light of the nature of a short review/editorial, while we include the key unique data in the current manuscript, we will try to report more detailed data regarding control of the patients with alternate intra-op MCS in a separate manuscript in the near future.

Reviewer E

Comment 1: In this brief communication Dr. Shigemura reviews their experience with intraoperative peripheral VA ECMO at Temple. It's certainly an important topic and the individual sections of the paper are nicely written. I have the following comments:

1) The manuscript seems to veer away from describing the experience with peripheral VA-ECMO, with several sections instead describing outcomes among patients with peripheral vascular disease and AAA. I would suggest re-structuring the outline of the manuscript to align better with the stated goal of describing the experience with peripheral VA-ECMO. Specific recommendations:
a) I would keep the introduction as-is, describing the rationale for intraoperative VA ECMO including potential benefits/risks of peripheral vs central
b) Next I would review your center's protocol for determining whether peripheral VA ECMO is appropriate for a given candidate (CT protocol, etc).
c) Next I would present the demographics of pts who received peripheral vs central VA ECMO (or CPB, if used). This could potentially be in table format as a replacement for table 3
d) Next I would present the complications encountered in peripheral vs central VA ECMO, including the incidence of differential hypoxemia with the former.
e) Finally, the authors could have one section on their experience in patients with PAD and/or AAA. I assume these were all managed intraoperatively with central VA ECMO but this should be clearly stated.

Response 1: According to the reviewer's suggestions, we have reorganized the main text by changing the

orders of the sections. Following the introduction, we first allude to the increasing role of peripheral VA ECMO approach. Since those who underwent central VA ECMO cannulation due to severe PAD were only three patients at our center, we decided to keep the current Table 3 while those cases are addressed in more clear manner in the text of subsection 'PAD' under the section of 'Preop CTAP assessment' which is essentially in the center of our current protocol for determining intraoperative MCS approach.
This CTAP assessment also involves the concurrent risk stratification of AAA. While both PAD and AAA share their aortic pathology and co-existence of PAD can increase risks for AAA rupture, we delineate their contribution to mortality at the end of the section.
After all the points related to PAD are duly discussed, we move to a separate major concern for differential hypoxemia and develop the discussion under a separate section. Thank you very much for all the precise advice.

Comment 2: Line 90: "Preoperative CT assessment plays a key role in preventing peripheral vascular complications during91 lung transplantation"; I don't think this heading accurately describes the authors' findings. Also see above – I would review your center's approach to pre-transplant imaging and decision making regarding peripheral vs central VA ECMO separately (prior to presenting the outcomes). But rather that the CTs "preventing complications", I think it's more appropriate to simply say that they helped guide the decision-making.

Response 2: According to the reviewer's suggestions, we revised the heading of the section by adding to decision making on intraoperative MCS approach.

Comment 3: Which patients under the age of 65 underwent CTs? Please provide specific criteria (expand on "cardiovascular or metabolic comorbidities"

Response 3:
Due to the insurance coverage, currently CTAP for PAD assessment is available only for those aged above 65. While there has been a steadily increase in the number of lung transplant recipients who are older than 70 years of age, in aging population, many patients have multiple diseases characterized by acceleration of the normal aging process, such as cardiovascular disease including PAD. Our preliminary data also supported the correlation between PAD and suboptimal transplant outcomes among the elderly patients, as a part of the programmatic project with geriatric lung transplantation. Given together, we focused on those aged above 70 with PAD as high-risk group.
From this point of view, I'd concur with the reviewer that indication for CTAP and PAD assessment should be extended to the patients below 65 who have severe coronary artery disease and/or outstanding metabolic diseases such as diabetes mellitus and morbid obesity, referring to metabolic syndrome. Thank you very much for the valuable suggestions.

Comment 4: Consider a cartoon image to show the different cannulation strategies. For non-surgeons it may also be helpful to provide intraoperative photos with peripheral vs central cannulation, to show how visualization may be better with the former.

Response 4:
Since this is a short review/editorial, given the limited number of the tables and figures, we will focus on the current format while a reference demonstrating such a cartoon image to show the differences in cannulation strategies is added (please see a reference 1).

Reviewer F:

Comment 1: Congratulation to Authors for this very well written paper.
English and methodology are correct.
The subject is very interesting and well detailed in the article.

Response 1: Thank you for your comments.