Peer Review File

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Reviewer A

The authors demonstrated the risk factors of PGD after lung transplantation for ARDS and chronic respiratory diseases. I have some comments.

Comment: The authors should discuss more about how they will manage ARDS patients and chronic respiratory diseases differently in order to prevent severe PGD, based on the current study results.

- Thank you. In our center, the management of post lung transplant for ARDS patients and chronic respiratory diseases patients is same and management has been standardized which include induction immunosuppression regimen: Basiliximab 20mg (intra-op and POD 4) and Methylprednisolone 1000mg (intra-op), maintenance immunosuppression regimen: Prednisone 0.5mg/kg PO daily from POD 1, Mycophenolate mofetil 1000mg BID from start POD 1, and Tacrolimus start POD 1. Goal target levels 8-12. We added our management in the Methods Section. (see page 7, lines 173-183)

"2.3 Immunosuppression management

Induction:

1. Methylprednisolone 1000mg via intravenous at intraoperatively and
2. Basiliximab 20mg at intraoperatively and postoperative day (POD) 4

Maintenance Immunosuppression:

1. Prednisone 0.5mg/kg PO daily from POD 1. Maximum dose = prednisone 40 mg daily. 0.5mg/kg daily for 1 month, then taper by 5mg every 2 weeks down to 5mg/day as a maintenance dose.
2. Mycophenolate mofetil 1000mg BID from POD 1.
3. Tacrolimus start POD 1. Goal target levels 8-12 within first year post-transplant; then target 8-10 thereafter"

Comment: The authors should ask a statistician to check the current study design and statistical analysis.

- Thank you. We have involved a statistician, Yuanqing Yan PhD, to check the study design and statistical analysis and have added him as a co-author.

Comment: The authors should describe limitations of this study.

- We added the following limitations to our study, in the Discussion Section. (see page 11-12, lines 292-298)

"Our study comes with limitations. Firstly, we studied patients at a single center, at Northwestern Memorial Hospital, which may limit the generalizability of our conclusions. Also, the number of patients studied were small, which may reduce statistical power. Furthermore, since these results are based on the experiences of a small cohort in a single large institution, differences in patient referral patterns, ECMO management standards, and eligibility criteria cannot be generalized and must be considered. Second, ARDS patients included a very wide variety of diagnoses such as severe bacterial pneumonia, COVID-19 infection, and others which could impact the statistical analysis results."

Comment: A lot of units have been missing in the text and Tables. (see Tables 1-6)

- Thank you. We have added the missing values.

Reviewer B

The authors present a retrospective analysis of risk factors for PGD Grade 3 among 250 patients transplanted for chronic lung diseases, and 43 patients transplanted for ARDS. Out of the non-ARDS patients, 24 (9.6%) developed PGD Grade 3. Out of the ARDS patients, 13 (30.2%) developed PGD Grade 3.

The biggest problem with this study is that the small number of subjects in the ARDS group, with only 13 cases of PGD3 observed, renders the statistical approach invalid. A multivariable logistic regression requires a minimum of 5 cases per variable included in the model, ideally at least 10. Even the much larger non-ARDS group, which has 24 cases of PGD3, does not have sufficient numbers to meet this basic validity criterion. As such, the model constructed on the basis of such a small number of subjects/cases is uninterpretable.

- Thank you. We added them in the limitation. As for univariate and multivariate models have been established. Below we have highlighted prior publications on this. (see page 11-12, lines 292-298)

1. Kurihara C, Walter JM, Karim A, Thakkar S, Saine M, Odell DD, et al. Feasibility of Venovenous Extracorporeal Membrane Oxygenation Without Systemic Anticoagulation. Ann Thorac Surg. 2020;110(4):1209-15.

2. Toyoda T CE, Manerikar A, et al. Recipient, donor and surgical factors leading to

primary graft dysfunction after lung transplant. Journal of Thoracic Disease. 2023.

3. Kurihara C, Manerikar A, Gao CA, Watanabe S, Kandula V, Klonis A, et al. Outcomes after extracorporeal membrane oxygenation support in COVID-19 and non-COVID-19 patients. Artif Organs. 2022;46(4):688-96.

4. Manerikar A, Watanabe S, Kandula V, Karim A, Thakkar S, Saine M, et al. Indwelling Central Venous Catheters Drive Bloodstream Infection During Veno-venous Extracorporeal Membrane Oxygenation Support. Asaio j. 2022;68(6):859-64.

Other issues surrounding the statistical approach include the strategy for variable selection, which ideally should be based on known causal associations, as might be illustrated with the aid of a directed acyclic graph (an approach which the authors may consider if they are able to expand the current study with more included subjects).

- Thank you. Please see above comments.

The limitations of the study need to be addressed in the discussion section. Unexpected findings, such as the fact that ischemic time is not associated with PGD in the ARDS group, should also be discussed. The authors state that "prolonged ischemic time exacerbates ischemia reperfusion injury" – so why would this not be the case in the ARDS group? (I suspect this is a result of the small number/inadequate methodology, but if presenting the results as valid, findings of this nature need to be addressed.)

- Thank you. We have added the limitations. (see page 11-12, lines 292-298)

Minor comments

• The correct term for the analysis used here is "multivariable", as "multivariate" refers to models which incorporate multiple dependent variables, which is not the case here.

• Case numbers of the primary outcome (PGD3) should be presented in the text in the tables presenting regression analysis results.

• Tables should be presented in the same order in which they are referenced in the text.

- Thank you. We have added and modified the text based on above comments.
(see page 3 lines 68 and 71, page 8 lines207, page 10 lines 251 and 262)
(see Table 1-6)

Reviewer C

Why t-test for PGD rate ARDS vs no ARDS, instead of OR for ARDS?

- Thank you. Odds ratio is used in the Univariate and Multivariate logistic regression analysis.

Pre-transplant and pre-transplant used interchangeably during text, lose capital letters when not in the beginning of a sentence.

- Thank you. We have fixed this.

Discussion about albumin: The pre-transplant condition of these patients, characterized by heightened inflammation and compromised nutritional status reflected in albumin levels, plays a pivotal role in their susceptibility to PGD. --> can just as well be said about patients with chronic respiratory failure.

- Yes, that could be occurring in patients with chronic respiratory failure, but we believe ARDS patients have more acute events and more prominent in those with inflammation and compromised nutritional status compared to patients with chronic respiratory failure.

Could you provide survival curve for ARDS vs non-ARDS? Difficult to know what the length of follow-up was in this study.

- Thank you. Figure 1 represents the survival curve for ARDS vs non-ARDS. (see Figure 1)

Reviewer D

This is a very well-written article that has statistically robust findings and is well delivered. However, the fundamental issue here is differentiating ARDS and PGD3. Given that patients with more patients ARDS were already on MCS, and hitherto had a lower albumin, this study infers an association of patient acuity and likelihood of PGD3 more than ARDS and PGD3.

The bias here is perhaps due to the already established MCS pre-operatively, alongside the longer ischaemic times (given the double lung transplant status). ARDS is a sequela of an insult that has multiple causes, from simple aspiration to a florid infection.

- Thank you. We have added these comments in the limitation section. (see page 11-12, lines 292-298)

If we are discussing post-COVID ARDS, however, then the study merely highlights the improvements noted once the disease had run its course and the more pertinent questions are

whether or not vaccinations were administered, etc. To merge ARDS as a precursor is perhaps ambitious given its multifactorial etiology of it. This compiled with the multifactorial etiology of PGD Lung is a recipe for disaster. Unfortunately, I think the research question is flawed from its inception and therefore not remediable.

- We recognize that the questions raised by the reviewer are broadly relevant but were not within the scope of the current study. Our study objective was to determine the predictors of PGD following transplantation in patients with acute and chronic respiratory failure. We recognize that ARDS has a broad etiology but several studies have now revealed that it follows a common pathogenesis. Hence, our rationale to evaluate predictors of PGD in patients with ARDS and chronic end-stage lung diseases is justified.