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Reviewer A

• Overall

o This is a retrospective study utilizing an institutional dataset to explore risk factors associated with PGD. Although many papers have previously attempted to identify risk factors associated with PGD, the proposed novelty in this analysis is that it distinguishes the clinical severity of PGD and seeks to find predictors of Grade 1 and 2 PGD and Grade 3 PGD separately. In univariate analysis, they identified several recipient factors including, lower age, lower albumin, higher serum bilirubin, as well as several intraoperative factors including, operative time, transfusion of blood products, and ischemic time that were associated with Grade 3 PGD. Operative time was also associated with Grade 1 and 2 PGD in both univariate and multivariate analysis. However, interpreting this operative time variable would be easier if we had information about potential confounders like previous cardiothoracic surgery or prior lung transplant. Additionally, the authors do not identify specific risk factors associated with Grade 3 PGD in multivariate logistic regression analysis. This weakens the rationale for this analysis as it could imply that there are not unique factors that would predict severe PGD, but rather just factors that predict PGD generally.

Comment 1:

- However, interpreting this operative time variable would be easier if we had information about potential confounders like previous cardiothoracic surgery or prior lung transplant.

Reply 1:

- **Thank you so much for reviewing our manuscript. None of the recipients had prior cardiac surgery or lung transplant. We have added a sentence referring to this (page 10, line 4-5). The other reviewer asked about the history of pleurodesis. We did not have enough information on it but added a sentence on the topic in the Discussion section (page 16, lines 19-21).**

Change in the text:

- (Page 10, lines 4-5) All recipients had no prior history of cardiac surgery or LT.
- (Page 16, lines 19-21) Furthermore, there was a lack of information regarding

a history of pleurodesis. This factor can also potentially increase operative time and blood loss.

Comment 2:

- Additionally, the authors do not identify specific risk factors associated with Grade 3 PGD in multivariate logistic regression analysis. This weakens the rationale for this analysis as it could imply that there are not unique factors that would predict severe PGD, but rather just factors that predict PGD generally.

Reply 2:

- **Thank you for pointing this out. Due to the relatively small sample size, we were unable to find independent factors in the multivariate logistic analysis model. But, we do not believe this weakens the rationale for this analysis. It means that the factors found in the univariate logistic analysis were confounded and could not indicate independent factors in the multivariate logistic analysis model. By narrowing down the factors calculated in the univariate to those that can be intervened upon and further analyzed, we believe that this study still could contribute to reducing PGD and improving survival.**

Change in the text:

- (None)

• Methods

Comment 3:

- It would be helpful to have more information about the cohort. For instance, were any patients being retransplanted?

Reply 3:

- **We appreciate you pointing this out. No re-lung transplant patients were included. We have added a sentence referring to this in the Results section (page 10, lines 4-5).**
-

Change in the text:

- (Page 10, lines 4-5) All recipients had no prior history of cardiac surgery or LT.

Comment 4:

- Were there differences in indications for transplant between the cohorts?

Reply 4:

- **This is a very important point. Bilateral or single lung transplant, pre VV-ECMO use, and etiology were added to the demographic table for analysis: PGD grade 3 was more prevalent in COVID-19-associated ARDS; PGD grades 1 and 2 were seen in PAH; and, PGD group 0 had a higher proportion of COPD. We have added a sentence in the Results section (page 10, lines 15-18).**

Change in the text:

- (Page 10, lines 15-18) Coronavirus disease 2019 (COVID-19) associated acute respiratory distress syndrome (ARDS) was a more common indication for LT in PGD grades 1 to 3 than PGD grade 0 (grade 0 vs 1 or 2 vs 3, 10.8% vs 28.9% vs 34.8%, p<0.01).

Comment 5:

- Were any patients on ECMO prior to transplant?

Reply 5:

- **We appreciate you pointing this out. Preoperative VV-ECMO was used in 6% of patients with PGD grade 0, 11.1% of patients with PGD grade 1/2 and 52.2% of patients with PGD grade 3. We added this into the main Manuscript (page 10, lines 12-14).**

Change in the text:

- (Page 10, lines 12-14) More VV-ECMO was used before LT in PGD grade 3 than in the other groups, and more bilateral LT were performed in PGD grades 1 to 3 (grade 0 vs 1 or 2 vs 3, pre VV-ECMO use, 6.0% vs 11.1% vs 52.2%, p<0.001; bilateral, 54.2% vs 84.4% vs 73.9%, p<0.01; respectively).

Comment 6:

- For the grade 3 PGD cohort, it would be helpful to know how many patients were on ECMO versus how many qualified based on PaO2/FiO2 ratio.

Reply 6:

- **This is a great point. Of the 23 patients with PGD grade 3, 21 of them were supported with ECMO after LT, and 2 patients were graded PGD grade 3 based on low PaO_2/FiO_2 ratio without ECMO. We have added a sentence referring to this (page 10, lines 7-9).**

Change in the text:

- (Page 10, lines 7-9) Of the 23 patients with PGD grade 3, 21 of them were supported with ECMO after LT, and 2 patients were graded PGD grade 3 based on the low PaO2/FiO2 ratio without ECMO.

Comment 7:

- The neurological dysfunction variable seems to be just capturing stroke. Unless it includes other complications as well, it would be clearer to just group these complications as stroke instead.

Reply 7:

- **Thank you for pointing this out. We have changed the terminology from neurological dysfunction to stroke (page 8, lines 12-15).**

Change in the text:

- (Page 7, lines 12-15) *Stroke*
- Stroke was defined as a new deficit confirmed via abnormal neuroimaging, (either computed tomography scan or magnetic resonance imaging), which was confirmed by a neurologist. This was further divided into ischemic or hemorrhagic causes.

• Results

Comment 8:

- It would be helpful to have some insight into the differences in operative time between Grade 0 and Grade 1 and 2 PGD. Are these factors that the surgical team can modify or are these reflective of factors like prior surgery/transplant that cannot be changed.

Reply 8:

- **This is a great point. We added the preoperative VV-ECMO use, laterality of lung transplant, etiology, intraoperative VA-ECMO use and VA-ECMO time to tables 1 and 2.**
- **According to the demographic and intraoperative results tables, there were more bilateral lung transplant and intraoperative VA-ECMO use in the PGD grade 1/2 groups. As a result, ischemia time and operative time appeared to be longer than in the PGD grade 0 group.**
- **We added this information in the main Manuscript (page 10, lines 12-14, and page 11, lines 6-8).**

Change in the text:

- (Page 10, lines 12-14) More VV-ECMO was used before LT in PGD grade 3 than in the other groups, and more bilateral LT were performed in PGD grades 1 to 3 (grade 0 vs 1 or 2 vs 3, pre VV-ECMO use, 6.0% vs 11.1% vs 52.2%,

p<0.001; bilateral, 54.2% vs 84.4% vs 73.9%, p<0.01; respectively).

- (Page 11, lines 6-8) Intraoperative veno-arterial extracorporeal membrane oxygenation (VA-ECMO) was used more frequently in PGD grades 1 to 3 (grade 0 vs 1 or 2 vs 3, 45.8% vs 82.2% vs 82.6%, p<0.001). However, the length of VA-ECMO time did not impact the developing PGD (p=0.74) (Table 2).

Comment 9: For the blood transfusion findings, would be useful to include whether all transplants were performed on CPB or whether some were done on ECMO.

Reply 9:

- **Thank you for pointing this out. We used only central VA-ECMO for the patients, if necessary, because previous publications showed that VA-ECMO use decreased blood transfusion during lung transplant compared to CPB use.**
- **Our policies for mechanical support have been added to the Discussion section (page 15, lines 18-19).**

Change in the text:

- (Page 15, lines 18-19) Based on these findings, we applied central VA-ECMO instead of CPB to all patients in this study cohort.

Reviewer B

This is a retrospective single center study where the authors sought to determine the risk factors of primary graft dysfunction (PGD) grading following lung transplantation.

The study includes a total of 151 patients between 2018 and 2021, out of whom 23 patients experienced PGD3.

I read this paper with great interest.

Overall the manuscript is interesting and it includes some useful clinical information for the readers.

However, there are already numerous prior studies highlighting the risk factors associated with PGD following lung transplantation. In line with those findings, quite a few therapeutic ideas to prevent PGD have also been long proposed and tested while some of them have been incorporated into clinical practice including those that can play a potential role in PGD reduction such as the usage of ECMO as intraoperative

mechanical circulatory support, EVLP device as a platform for treating the donor lungs of marginal quality, or posttransplant management with pharmacological agents.

With these growing knowledge of PGD as well as evolving practice, PGD prediction models to aim at identifying more updated risk factors need to be better validated and then duly incorporated into clinical practice. From this point of view, can the authors elaborate where their model is different from the prior studies, and how they've handled such PGD-targeted therapies/strategies through their study which are already incorporated into clinical practice from statistics standpoints to duly validate the model?

Comment 10:

- From this point of view, can the authors elaborate where their model is different from the prior studies, and how they've handled such PGD-targeted therapies/strategies through their study which are already incorporated into clinical practice from statistics standpoints to duly validate the model?

Reply 10:

- **We appreciate your kind feedback regarding our manuscript. Our study is different from prior studies as it identifies individual risk factors of PGD grade 1 or 2 and 3. Previous studies were focused only on PGD grade 3. Therefore, we attempted to clarify the risk factor for PGD grade 1 or 2 and compare to grade 3. Also, we included all of the recipient, donor and surgical factors.**
- **In this study, we didn't include EVLP donors. In addition, we used central VA-ECMO for all of the patients, if necessary. We added a sentence referring to this (page 10, lines 3-4, and page 15, lines 18-19).**

Change in the text:

- (Page 10, lines 3-4) All donor lungs were donated after brain death, and no ex vivo lung perfusions were performed.
- (Page 15, lines 18-19) Based on these findings, we applied central ECMO instead of CPB to all patients in this study cohort.

Comment 11:

- Their results demonstrating that operative time was an independent risk factor for PGD development appear to be outstanding whereas their discussion concludes that reduction in operative time may not contribute to reducing the PGD incidences. Do the authors think that this inconclusive ending may be

attributed to their analysis without sufficient confounding variables?

Reply 11:

- **Thank you for pointing this out. This study is not a warning rushed surgery aimed at reducing operative time.**
- **I changed the sentence to the following (page 16, lines 11-13).**

Change in the text:

- (Page16, lines 11-13) Therefore, this study is not a recommendation to simply reduce operative time. Further studies are needed to clarify the relationship between these factors that can increase operative time and PGD.

Comment 12:

- Prolonged operative time may be associated with early sign of PGD requiring escalated and/or prolonged intraoperative mechanical circulatory support, as a consequence of more complex cause-and-effect relationships. This also needs to be more precisely discussed.

Reply 12:

- **This is a very important point. The use of central VA-ECMO was added as a variable and analyzed.**
  VA-ECMO use was more common in PGD 1-3 cases. In fact, intraoperative use of VA-ECMO significantly increased operative time in our cohort (non-VA-ECMO 6.2 ± 1.4 hours, VA-ECMO 8.1 ± 1.4 hours, $p<0.001$). We added a sentence referencing this (page 16, lines 6-13).
-

Change in the text:

- (Page 16, lines 6-13) However, operative time depends not only on the surgical technique but also on various factors such as the use of circulatory and respiratory support and the severity of adhesions. In fact, patients who were supported by VA-ECMO during lung transplant procedures had significantly longer operative times in our cohort (the data is not shown in the result; non-VA-ECMO 6.2 ± 1.4 hours, VA-ECMO 8.1 ± 1.4 hours, $p<0.001$). Therefore, this study is not a recommendation to simply reduce operative time. Further studies are needed to clarify the relationship between these factors that can increase operative time and PGD.

Reply 13:

- Minor)

- 1. They used an oxygen saturation/FiO2 ration was used to calculate when standard PaO2/FiO2 ratio was not available. Is this consistent with the ISHLT guidance as well as the evidence in prior PGD studies?

Reply 13:

- **Thank you for pointing this out. This is consistent with the ISHLT guidelines.**

Change in the text:

- (None).

Reviewer C

Comment 14:

- Many thanks for the opportunity to review this manuscript.
- Abstract - reads well with a good overview and highlights significant results succinctly. The conclusions seem disjointed with operative time correctly identified but the following statement addressing Grade 3 PGD perhaps should be truncated as the study itself correctly highlights the lack of significant numbers to make a meaningful conclusion.

Reply 14:

- **Thank you for reviewing our manuscript. This is a great point. Following your suggestion, we deleted the sentence that addresses PGD grade 3 and simplified the conclusion of the abstract (page 2, lines 21-22).**

Change in the text:

- (Page 2, lines 21-22) Conclusion: The calculated predictors of primary graft dysfunction grade 1 or 2 were similar to those of PGD grade 3.

Comment 15:

- The introduction is well thought out and details the premise although we have moved away from the term bronchiolitis obliterans syndrome to Chronic Lung Allograft dysfunction as a broader term.

Reply 15:

- **Thank you for pointing this out. We changed the term "bronchiolitis obliterans syndrome" to chronic lung allograft dysfunction (page 5, lines 13-14).**

Change in the text:

- (Page 5, lines 13-14) In addition to early mortality, PGD could lead to late mortality including chronic lung allograft dysfunction.

Comment 16:

- The methods are meticulously written. AKI was defined using the RIFLE criteria.
- The results are presented well.
- Issues
- 1) recipient details - other surgical factors such as prior pleurodesis have been known to increase PGD rates. have these been considered? if not, it should be mentioned under surgical factors for PGD

Reply 16:

- **This is an excellent point. We haven't captured prior pleurodesis and added a sentence referencing this in the Discussion session (page 16, lines 19-21).**

Change in the text:

- (Page 16, lines 19-21) Furthermore, there was a lack of information regarding a history of pleurodesis. This factor can also potentially increase operative time and blood loss.

Comment 17:

- 2) Any patients on VV ECMO preop?

Reply 17:

We appreciate you bringing this up. We added preoperative VV-ECMO use as a variable of our analysis and re-summarized our data in table 1. Preoperative VV-ECMO was used in 6% of patients with PGD grade 0, 11.1% of patients with PGD grade 1/2, and 52.2% of patients with PGD grade 3. We added a sentence (page 10, lines 12-14).

Change in the text:

- (Page 10, lines 12-14) More VV-ECMO was used before LT in PGD grade 3 than in the other groups, and more bilateral LT were performed in PGD grades 1 to 3 (grade 0 vs 1 or 2 vs 3, pre VV-ECMO use, 6.0% vs 11.1% vs 52.2%, $p<0.001$; bilateral, 54.2% vs 84.4% vs 73.9%, $p<0.01$; respectively).

Comment 18:

- 3) the Grade 3 recipients were younger but appear to be more acutely unwell, more anemic, higher bilirubin and BUN - which raises the issue of haemolysis - were these patients on support?

Reply 18:

- **Thank you so much for bringing this up. Half of the patients with PGD grade 3 had preoperative VV-ECMO use (page 10, lines 12-14). That may be the cause of the abnormal lab values.**

Change in the text:

- (Page 10, lines 12-14) More VV-ECMO was used before LT in PGD grade 3 than in the other groups, and more bilateral LT were performed in PGD grades 1 to 3 (grade 0 vs 1 or 2 vs 3, pre VV-ECMO use, 6.0% vs 11.1% vs 52.2%, p<0.001; bilateral, 54.2% vs 84.4% vs 73.9%, p<0.01; respectively).

Comment 19:

- 4) Line 25, -page 8 Discussion - 'operative time correlated with ischaemic time'

- The issue I have with operative time is that it is nonspecific. Ischaemic time is rather specific in that it refers to ischaemia followed by time to reperfusion. For operative time, patients with prior surgery to the chest or VV-ECMO, cystic fibrosis have a more challenging dissection period which prolongs ischaemic time. This would have a major bearing compared to a prolonged operative time because a routine lung transplant prolonged due to increased travel time but in 'less acute' recipients.

- I therefore do not think operative time should be a variable as it does not inform me as a surgeon on whether prolonged ischaemic time (which is a known cause of PGD) vs complex surgical dissection due to previous pleurodesis or LVRS is the reason for the prolonged operative time.

Reply 19:

- **Thank you for pointing this out. Operative time is defined as skin incision to skin closure. We believe that a longer operative time is still informative because the ischemic time may be longer due to the need to wait for implantation after donor lung arrival at the hospital.**
- **We added etiology into the analysis of this study, but we were unable to**

find that CF had an impact on the incidence of PGD.

Change in the text:

- (None)

Comment 20:

- Additional blood transfusions highlight complex surgical dissection and bleeding as well and can cause TRALI which I appreciate will be difficult to differentiate on CXR. Cell salvage techniques have their own issues as they can increase the transfusion rate of platelets and FFP.
- It would be prudent to highlight surgical factor differences as well such as how many were implanted via ECMO vs CPB.

Reply 20:

- **Thank you for pointing this out. We agree with you that cell salvage is controversial. We deleted the sentence referring to it.**
- **We used only central VA-ECMO for lung transplant procedures. We added a sentence referring to this (page 15, lines 11-14).**

Change in the text:

- (Page 15, lines 11-14) Blood transfusion volume may be associated with blood loss, operative time, and use of VA-ECMO during LT. In this study, higher red blood cell transfusions showed an association with a higher grade of PGD. Actually, the ISHLT recommends minimizing blood transfusion during LT.

Comment 21:

- Given this is a single centre study, I would like to see further details
- 1) recipient aetiology - COPD vs CF vs others

Reply 21:

- **This is a great point. We added etiology as variables in table 1 of our analysis.**

Change in the text:

(None)

Comment 22:

- 2) surgical incision - sternotomy vs clamshell vs anterior/posterior thoracotomy

Reply 22:

- **Thank you for pointing this out. All bilateral lung transplants were performed via clamshell incisions, and all single lung transplantations were performed via anterior thoracotomies.**
- **We added a sentence referencing this in the Methods section (page 6, lines 5-7).**

Change in the text:

- (Page 6, lines 5-7) All bilateral lung transplants were performed via clamshell incisions, and all single lung transplantations are performed via anterior thoracotomies.

Comment 23:

- 3) single vs double lung

Reply 23:

- **This is an excellent point. We added bilateral lung transplantation as a variable for our analysis.**
- **We added a sentence referring to this (page 10, lines 12-14).**

Change in the text:

- (Page 10, line 12-14) More VV-ECMO was used before LT in PGD grade 3 than in the other groups, and more bilateral LT were performed in PGD grades 1 to 3 (grade 0 vs 1 or 2 vs 3, pre VV-ECMO use, 6.0% vs 11.1% vs 52.2%, $p<0.001$; bilateral, 54.2% vs 84.4% vs 73.9%, $p<0.01$; respectively).

Comment 24:

- 4) Height and weight mismatch between donor and recipient if any

Reply 24:

- **Thank you for pointing this out. We don't have these data.**

Change in the text:

- (None).

Comment 25:

- 5) MCS usage

Reply 25:

- **We appreciate you bringing up this needed clarification. We added preoperative VV-ECMO use and intraoperative central VA-ECMO use as variables for our analysis and found the independent factor for PGD grade 1 or 2.**
- **We added some sentences related to this (page 13, line 16 -page 14, line 1).**

Change in the text:

- (page 14, line 16 -page 15, line 1) The results of univariate analysis showed that bilateral lung transplant cases, etiology of COVID-19 associated ARDS, and PAH, operative time, ischemic time and intraoperative VA-ECMO use may be risk factors affecting PGD grade 1 or 2. On the other hand, recipient age, preoperative VV-ECMO use, bilateral lung transplant cases, etiology of COVID-19 associated ARDS, hemoglobin count, platelet count, BUN, albumin, total bilirubin, PaO_2 levels on the day of transplant, operative time, intraoperative blood transfusion volume, and intraoperative VA-ECMO use could be related to PGD grade 3. Multivariate analysis showed that intraoperative VA-ECMO use was an independent risk factor for the development of PGD grade 1 or 2, but no significant independent risk factor for the development of PGD grade 3 was found.

Comment 26:

- 6) DBD vs DCD lungs (if the centre has a DCD program)
- 7) EVLP usage - if done

Reply 26:

- **Thank you so much for bringing this up. All donors were DBD, and EVLP donors were not included in this study. We added a sentence referring to this in the Results section (page 10, lines 3-4).**

Change in the text:

- (Page 10, lines 3-4) All donor lungs were donated after brain death, and no ex vivo lung perfusions were performed.

Reviewer D

Comment 27:

- Recipient, donor, and surgical factors leading to primary graft dysfunction after lung transplant
- General comments:
- As acknowledge by the authors, this single center study suffers from the small number of PGD cases. This makes it hard to further analyse the association of each PGD subcategory with potential risk factors. A mutlicenter study or a national/ international database study would allow more convincing conclusions.
- Specific comments:
- The stated goal of the objectives of this study is as follows: ‘we sought to identify recipient, donor, and surgical risk factors specifically associated with mild/moderate or severe PGD’ (Page 3 Lines 14-15).

- [1] The authors stated in the Discussion section-'Recipient factors such as gender, race, obesity, sarcoidosis as the primary disease, and primary hypertension were risk factors.' (Page 8 lines 4-5) Recipient diagnosis, is therefore one of the factors related to PGD, particularly PAH and sarcoidosis. However, the manuscript does not provide any information about the recipient diagnosis for the PGD patients in the table of patient characteristics. Furthermore, in the univariate (and multivariate) analysis, 'Recipient diagnosis' is not one of the variable being analysed, such as 'PAH yes/no', or 'sarcoid yes/no'.
- I strongly suggest the authors provide this information in the revised manuscript.

Reply 27:

- **We appreciate your kind feedback regarding our manuscript. We added etiology as a variable for our analysis, and there were no sarcoidosis cases in this study. PAH and COVID-19-associated ARDS were risk factors for PGD grade 1 or 2 in univariate logistic analysis; and only COVID-19-associated ARDS was related to PGD grade 3 in univariate analysis.**
- **We added some sentences referring to these results (page 12, lines 2-4, and lines 16-21).**

Change in the text:

- (Page 12, lines 2-4) Bilateral lung transplant cases, etiology of COVID-19 associated ARDS, and pulmonary arterial hypertension (PAH) were more common in PGD grade 1 and 2 groups.
- (Page 12, lines 16-21) The results showed that the PGD grade 3 group had significantly younger recipients, more frequent preoperative use of VV-ECMO, more COVID-19-associated ARDS, lower hemoglobin, platelets, and albumin; and higher BUN and total bilirubin in laboratory tests, lower PaO_2 in arterial blood gas analysis, longer operative time and ischemic time, higher blood transfusion use, and more frequent preoperative use of VA-ECMO.

Comment 28:

- [2] Intraoperative outcomes (page 6, lines 14-18). Longer ischemic times and larger volumes of blood product transfusion are surrogates for the difficulty encountered during the explant and implantation.

Reply 28:

- **Thank you for bringing this to our attention. We agree with this comment.**

Change in the text:

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- (None).