

## Peer Review File

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### Reviewer A

Outcome of lung transplantation for end-stage 1 pulmonary diseases with pulmonary hypertension: A single-center experience

#### Summary:

In this manuscript, the authors retrospectively review outcomes after single or double lung transplantation in a cohort of patients from China with end stage lung disease and pulmonary hypertension. They cite differences in population characteristics and culture as a rationale to study outcomes in this specific cohort. The authors conclude that short- and medium-term survival outcomes are similar in recipients undergoing SLT or DLT and that recipients >60 years old have worse survival.

#### Minor revisions:

1. Introduction, page 3, line 4

a. The sentence beginning with “Lung transplantation in China...” needs clarification.

Response: Thank you very much for the comments on our work and all suggestions for improvement. The sentence came from “Ann Transl Med 2020;8(3):41”.

2. Introduction, page 3, line 11

a. The definition of pulmonary hypertension has changed.

b. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019 Jan 24;53(1):1801913. doi: 10.1183/13993003.01913-2018. PMID: 30545968; PMCID: PMC6351336.

Response: Thank you very much for the comments. Most similar studies had used the old definition of pulmonary hypertension. We also used the old version in order to compare the results.

3. Introduction, page 3, line 12

a. Consider adding a reference regarding PH and development of PGD

b. Kuntz CL, Hadjiliadis D, Aha VN, Kotloff RM, Pochettino A, Lewis J, Christie JD. Risk factors for early primary graft dysfunction after lung transplantation: a registry study. Clin Transplant. 2009 Nov-Dec;23(6):819-30. doi: 10.1111/j.1399-0012.2008.00951.x. Epub 2009 Feb 20. PMID: 19239481.

Response: Thank you very much for your suggestion. We added the reference.

4. Introduction, page 3, line 22

a. Lung transplantation should be singular not plural here.

Response: Thank you very much for your suggestion. We have corrected it.

5. Materials and methods, recipient selection, page 4, lines 17-19

a. This sentence should be edited. Consider these edits below:

b. "These patients should be referred to a lung transplant center early so that patients have..."

c. "...and the transplant center can evaluate them in detail and optimize their..."

Response: Thank you very much for your suggestion. We have corrected it.

6. Materials and methods, recipient selection, page 4, lines 19-21

a. This sentence should also be edited. Consider these edits below:

b. "However, these patients were often referred in a deteriorating disease state in which they could not tolerate the necessary evaluation"

Response: Thank you very much for your suggestion. We have corrected it.

7. Materials and methods, Procedure and donor selection, page 5, line 4

a. Consider rewording this sentence. Change BLT to DLT to maintain the same acronym throughout the manuscript.

b. "Given the abundance of lung donors in China, disease and patient factors were more important than donor availability in choosing between SLT and DLT."

Response: Thank you very much for your suggestion. We have corrected it.

8. Materials and methods, Surgical technique, page 5, line 19

a. Remove "with"

Response: Thank you very much for your suggestion. We have corrected it.

9. Materials and methods, Surgical technique, page 5, line 21

a. Change "and" to "or" and remove the word "obviously"

Response: Thank you very much for your suggestion. We have corrected it.

10. Materials and methods, Postoperative care and follow up, page 6, line 13

a. Change "extubate" to "extubated"

Response: Thank you very much for your suggestion. We have corrected it.

11. Results, Preoperative characteristics, page 7, line 9

a. Change to "From March 2016 to December 2019..."

Response: Thank you very much for your suggestion. We have corrected it.

12. Results, Intraoperative outcomes, page 8, line 8

a. Change to "...was shorter for right lung than for left lung."

Response: Thank you very much for your suggestion. We have corrected it.

13. Results, Intraoperative outcomes, page 8, line 3

a. Change to "Three patients suffered from atrial fibrillation in total, two after clamping the pulmonary artery and one after clamping the left atrial wall."

Response: Thank you very much for your suggestion. We have corrected it.

14. Results, Postoperative outcomes, page 8, line 19

a. Change to "Three patients required re-thoracotomy..."

Response: Thank you very much for your suggestion. We have corrected it.

15. Results, Postoperative outcomes, page 9, line 5

a. Change "Compare" to "Compared"

b. Change "...the percentage of..." to "...percent predicted..."

Response: Thank you very much for your suggestion. We have corrected it.

16. Discussion, page 9, line 15

a. Change "...failed to standard..." to "...failed standard..."

Response: Thank you very much for your suggestion. We have corrected it.

17. Discussion, page 10, line 17

- a. Change BLT to DLT to maintain the same acronym throughout the manuscript.
18. Discussion, page 11, line 9
- a. Change to “A recent UNOS analysis revealed...”
- Response: Thank you very much for your suggestion. We have corrected it.
19. Discussion, page 11, line 15
- a. Change to “But a recent UNOS analysis concluded...”
- Response: Thank you very much for your suggestion. We have corrected it.
20. Discussion, page 12, line 6
- a. Change “hadn’t” to “did not have”
- Response: Thank you very much for your suggestion. We have corrected it.
21. Discussion, page 12, line 8
- a. Change to “Being severely underweight is related to...”
- b. Include a reference to for this statement.
- Response: Thank you very much for your suggestion. We have corrected it.
22. Discussion, page 12, line 12
- a. Change “hadn’t” to “did not have a..”
- Response: Thank you very much for your suggestion. We have corrected it.
23. Discussion, page 13, line 3
- a. Change “hadn’t” to “did not have”
- Response: Thank you very much for your suggestion. We have corrected it.
24. In Table 3, Change BLT to DLT to maintain the same acronym throughout the manuscript.
- Response: Thank you very much for your suggestion. We have corrected it.

Major revisions:

1. In the introduction, the authors should elaborate on the rationale of studying the Chinese population in this investigation, specifically regarding how the differences in “population characteristics and culture” could affect outcomes of SLT vs DLT. This is reviewed briefly in the discussion but should be elaborated in the introduction as well.  
Response: Thank you very much for your suggestion. Wu et al. (Annals of translational medicine 2020;8:41) and Hu et al. (Chinese medical journal 2019;132:2783-9) described the Chinese population. We cited these studies in the paper.
2. The authors should edit the “Materials and Methods” section to include only the methods they employed to design and execute the study.
  - a. In the “Recipient Selection” section, the authors discuss guidelines for referral and that, in their cohort, patients with a diagnosis of pulmonary hypertension were often referred at clinical deterioration rather than earlier in their disease. While this finding is important, it should be moved to the discussion section where the authors should elaborate on the implications of this finding both in their study and in the population at large.
  - b. In the “Procedure and donor selection” section, the authors should comment only that the decision to proceed with single versus double lung transplant was based on a variety of factors and made at the discretion of the transplant team. They should elaborate on the factors that influenced that decision in the discussion.
  - c. In the “Surgical technique” section, the authors should comment only on the surgical

techniques used for procedures in this study. The comments regarding the first SLT and the use of ECMO are better suited for the introduction or the discussion.

Response: Thank you very much for your suggestion. Indeed, these sentences should be moved from “Materials and Methods” section to introduction and discussion section. But it is easier to understand in this way.

3. Based on table 1, it appears that recipients undergoing DLT were younger and had higher mPAP. While this may have been by design, the effects of these differences between groups on postoperative outcomes should be discussed further.

Response: Thank you very much for your comments. We discussed these differences in discussion.

4. It appears that the majority of DLT in this cohort were performed in 2019, whereas SLT predominated prior to 2019 in this population. The authors should discuss the implications of this occurrence in their data. Were there differences in median follow up after lung transplantation between SLT and DLT? One major implication is that if median follow up was shorter for DLT patients, the long-term survival benefit of DLT in this population could have been missed.

Response: Thank you very much for your comments. The median follow up of SLT was longer than DLT patients, but the difference was not statistically significant.

5. The authors note that the absence of data on PGD was a limitation to the study. Given that this is one of the major sources of increased morbidity in this population, this is a major limitation. This should be discussed further. If available, this data should be included in the study.

Response: Thank you very much for your comments. The incidence of primary graft dysfunction were missing.

## **Reviewer B**

I read with interest your work titled “Outcome of lung transplantation for end-stage pulmonary disease with pulmonary hypertension: a single-center experience.” Please, read the following suggestions constructively:

### General comments

- The paper is focused and with interest in the field. However, it is needed a revision by an English native speaker. Also, improvements are required in the structure of the work.
- Please, may the authors check the correct use of abbreviations? (e.g., page 4 line 15, ISHLT is the first time used without the whole concept referenced)
- Do not use informal language, e.g., “couldn’t.”

Response: Thank you very much for your suggestion. We have corrected it.

### Introduction

- Page 3, line 8. May the authors update the incidence data of lung transplantations? In the current version, the data is to 2018.

Response: Thank you very much for your comments. We update the incidence data of lung

transplantations. The published version is to 2018.

- Page 3, lines 19-20. May the authors include the incidence of USA and Europe too?

Response: Thank you very much for your comments. Yes, it included the incidence of USA and Europe.

Material and methods

- Please, may you improve the structure of your work?

- Page 5, lines 1-2, lines 5-6. More details are needed. Please, specify all the criteria.

- Page 6, line 12. More drug information is necessary.

- Page 6. Please, include information about the follow-up. When? Where? And who was responsible?

Response: Thank you very much for your suggestions. We have improved it.

Results

- Page 7, lines 13-21. All the variables should be explained in M&M.

Response: Thank you very much for your suggestions. We have improved it.

- Page 8, line 2. Please, include the median, range, mean, and standard deviation in all-time variables.

Response: Data were presented as mean value with standard deviation (SD) or median with interquartile range (IQR) for continuous variables, and percentages for categorical variables.

- How was the influence of ECMO in the survival prognosis?

Response: Thank you very much for your comments. It was explained in the discussion (page 11, line 19-22 and page 12, line 1-5)

- Page 9, lines 8-11. Why did you compare younger patients than 60 years vs. older than 60? Please, justify in the introduction section. Also, for the rest of the sub-groups.

Response: Thank you very much for your comments. It was introduced in the discussion (page 11, line 6-14). And the survival curve had a larger difference when the cutoff was 60.

Discussion

- The first paragraph should highlight the most relevant of your results.

Response: Thank you very much for your suggestions. We have improved it.

Conclusions

- Why 30 days? Please, improve the results section to support this affirmation.

Response: Thank you very much for your comments. Mortality within 30 days was a variable which reflected postoperative short outcomes. Most perioperative mortality occurred within 30 days after surgery. And most studied described mortality within 30 days.

## **Reviewer C**

Lung transplantation is the therapy of choice for many end-stage lung diseases, and the presence of pulmonary hypertension certainly deserves special attention, considering the burden associated with this clinical problem.

Our comments and critics have the intention to contribute to your research project and facilitate comprehension for the reader.

We will describe our review in an item-by-item fashion:

Abstract:

1. we think you had to be clear in what you are planning to evaluate. Page 2- line 4, “analyze the outcomes of LTx for PH,” is confusing since you consider patients with ESLD with concomitant PH – not Primary PH.

Response: Thank you very much for your comments. We have improved it.

2. The other aspects of your abstract are appropriate, considering your aims.

Response: Thank you very much for your comments.

Introduction:

3. Page 3 – Line 11: please add a reference about your definition of PH.

Response: Thank you very much for your suggestions. We added a reference.

4. Page 3 – Line 15 to 18: that is where, it seems, your focus changed a bit because you mention, in our understanding, about primary PH- and it seems this is not the group you aim to evaluate.

Response: Thank you very much for your comments. It included primary PH and secondary PH.

5. Page 3 – Line 19: interesting and provocative thought because it is essential to have an idea about the particularities of the Chinese population. Thank you.

Response: Thank you very much for your comments.

Materials and Methods:

6. Page 4 – line 6: here, you still have not clarified the group you are planning to study. It seems confusing for the general reader.

Response: Thank you very much for your comments. This report describes the experience by comparing different procedures, age, mPAP, BMI, and indication of transplantation.

7. Page 4 – Line 14: you can certainly be more direct in your assumption.

Response: Thank you very much for your comments.

8. Page 5 – Line 1: you mention “economy,” and we found it very interesting but unexplored in your paper. How economy weights in when you are considering SLT or DLT? Perhaps you have local characteristics that can be important for us to learn and understand.

Response: Thank you very much for your comments. Economy was an important factor for considering SLT or DLT. The procedure was chosen jointly by both doctor and patients, SLT was relatively cheaper than DLT. Some patients may choose SLT because of lack of money. It was a pity that we did not offer local characteristics.

9. Page 5 – Line 6: Can you tell us why you choose SLT over DLT? We got your point, but this can be important for the reader.

Response: Thank you very much for your comments. Transplant procedures are worth studying. The best lung transplant procedures for patients with PH are still controversial. SLT and DLT had a significant impact on the survival.

10. Page 5 – Line 11: You mentioned you used Celsior or Low-Potassium Dextran. Were you capable of analyzing any difference in your results based on the preservation solution? Are you still using both? How did you choose? Did you replace one with the other over time?

Response: Thank you very much for your comments. I was not capable of analyzing the difference based on the preservation solution. Both of the solution was random used. We did not replace one with the other over time.

11. Page 5 – Line 17: Which ECMO configuration do you use? VA? VV? Other?

Response: Thank you very much for your comments. All VA, VV, and VV-A are used.

12. Page 6 – Line 12: Which additional drug therapy for PH was used after SLT? Can you extrapolate why?

Response: Thank you very much for your comments. Some patients used prostacyclin to decrease pulmonary artery pressure.

Results:

13. Page 7 – Line 10: you finally mention that you included “pts with secondary PH.” Now, this should be discussed before.

Response: Thank you very much for your comments. We have improved it.

14. Page 7 – Line 13: let us jump to your figure 1: you did many more COPDs SLT than COPDs DLT. Do you think this can affect your results? This is, in our opinion, a significant issue for your research.

Response: Thank you very much for your comments. It is worthy of further research.

15. Page 7 – Line 19: you mentioned for DLT, you had a “higher proportion of infectious disease,” which is quite apparent - you discussed elsewhere you did DLT for infection diseases.

Response: Thank you very much for your comments. DLT for infection diseases was suitable.

16. Page 8 – Line 22: you presented data that may not be relevant, like “time for anastomosis.” On the other side, relevant data like CLAD is not reported. Do you have any data on your CLAD incidence? That would be important.

Response: Thank you very much for your comments. It was a limitation that missing data on our CLAD incidence.

Discussion:

17. Here you discuss the controversial topic of SLT versus DLT. Please check if you have more recent references. Reference 20 is from 2009. And this is an ongoing discussion.

Response: Thank you very much for your comments. Reference 20 is not the primary reference.

18. Page 11 – Line 13: this paragraph seems confusing.

Response: Thank you very much for your comments. We have improved it.

19. Also, in this same paragraph, can you please explore your ECMO cannulation strategy. Your axillary approach seems interesting.

Response: Thank you very much for your comments. Yang et.al (reference 24) described the strategy in detail.

20. Page 12 – Line 12: In our view, and understanding regional particularities, it is an exciting approach to do SLT + jejunostomy. Frailty seems a contraindication in many centers, and it seems you are trying to tackle it. Perhaps, as you mentioned, you may receive patients for listing when they are extremely sick.

Response: Thank you very much for your comments.

Conclusions:

21. No comments. You bring together appropriately the things you aimed to discuss along with your paper.

Response: Thank you very much for your comments.

22. Figures 2, 3, and 4 are adequate.

Response: Thank you very much for your comments. I think figure 1 is useful.

23. Figure 5: don't you think it would be interesting to add SLT and DLT, especially regarding

your B and D?

Response: Thank you very much for your comments. Yes, it would be interesting to add SLT and DLT. But limited by the small sample size.

24. Your Tables are adequate, perhaps with too much data, sometimes with data that may not be so important.

Response: Thank you very much for your comments.

25. Table 3 – you described four patients using IABP. Can you explore the reasons?

Response: Thank you very much for your comments. Using IABP for patients with heart failure.

26. Table 3 – perhaps you could explore, along with the text, which types of bronchial anastomotic fistulas that you had and how did you manage them?

Response: Thank you very much for your comments. It should explore bronchial anastomotic fistulas in another topic.

In summary, your paper is interesting, but you fail to address the population of patients that you aimed to study initially adequately, and you only do that later on in the text. In addition, when you compare SLT and DLT, your groups are quite different. These are strong weaknesses of your project.

We appreciated the opportunity to review your paper, and we hope our contributions are going to be helpful for your future studies. But our impression, at this moment, is that you need a significant review of the structure and the data that you have for this study to be considered for publication.

Response: Thank you very much for your comments.

### **Reviewer D**

This paper reports on an observational study evaluating the outcomes in patients with pulmonary hypertension (PH) undergoing lung transplantation. The study includes a total of 63 patients for a study period between 2016 and 2019.

I read this with great interest.

However, aside from a small number of the patients enrolled in the study, in light of a subject which has been well addressed and extensively discussed for decades, the entire manuscript essentially reports their institutional experiences which don't appear to be consistent with the most recent or even more standardized current approach, and contains several major flaws.

First of all, their selection criteria for the surgical options, single versus double for those patients with PH remain unclear even after reading through the entire manuscript. They state that they 'were more inclined to perform single for older, severely underweight, and extremely ill patients'; however, those sick patients also tend to exhibit more significant PH, that is severe PH which requires a double. For those cases, what was their decision?

Response: Thank you very much for your comments. SLT confers short-term survival benefit but long-term harm, DLT confers short-harm but long-term survival benefit. The balance between short-term risk and long-term benefit is a crucial principle that decides SLT or DLT.



The authors also should be encouraged to elaborate their intraoperative ECMO strategy. They state in Discussion that they preferred ‘axillary artery-percutaneous femoral vein cannulation for VA ECMO’. Was this approach chosen for the single cases alone?

Response: Thank you very much for your comments. Yang et.al (reference 24) described the strategy in detail. This approach was not chosen for the single cases alone.

In addition, they state that this ECMO approach was extended postoperatively, referring to the experiences by the Hannover group (reference 24) whereas they used a different VA ECMO configuration with peripheral femoral artery/vein approach. Concerning the ECMO-associated thromboembolic risks in particular for stroke, axillar approach appears to be higher than femoral approach based on the previous literatures. Do they routinely use heparin drip for such postoperative extended VA ECMO cases? If they do, how soon do they start heparin to balance the risks for bleeding immediately postop with critically ill patients?

Response: Thank you very much for your comments. Low-dose heparin was used for part of patients. The timing of anticoagulation was determined by chest drainage.

In addition to their suboptimal 1-year survival with 65% for double and 73% for single as compared to those reported in the ISHLT Registry data (80-85%), their incidences of renal failure were also as high as 20% for single and 39% for double. The authors should explain this. According to many series of the prior ECMO literatures, ECMO is supposed to yield less incidences of renal insufficiency as compared to full cardiopulmonary bypass.

Response: Thank you very much for your comments. The included patients were older and severer. And this was a small sample study.

Lastly, it doesn’t appear to be appropriate for the authors to refer to the old data reported in the previous versions of the ISHLT Registry Report to justify their outcomes as well as the rationale in Discussion.

Response: Thank you very much for your comments. We have improved it.

The field of lung transplantation as well as the outcomes continue to evolve along with remarkable progress in the patients’ selection, management, surgical techniques, and technologies while those evolutions are duly updated annually in their official reports. From this standpoints, the authors should be advised to rewrite the Discussion by citing appropriate references in line with their group discussion and rationale.

Thank you for this privilege.

Response: Thank you very much for your comments. We have improved it.