

Peer Review File

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Reviewer 1

Comments to the authors:

I really appreciate editors to have provided me with a very valuable opportunity to get knowledge on the current status of lung transplantation in other country. I have some comments and questions as follows:

Major comments

Comment: The authors mentioned that the number of LT has increased since the incidence of humidifier disinfectant-associated interstitial lung disease. Do the authors still have a lot of patients suffered from ARDS due to humidifier disinfectant-associated interstitial lung disease? Where is humidifier disinfectant-associated interstitial lung disease included in the diagnosis on Table 1?

Reply: Thank you for the appreciation. In the past 3 years, no patient required lung transplantation due to humidifier disinfectant-associated interstitial lung disease. LTs because of humidifier disinfectant-associated interstitial lung disease mostly occurred between 2011 and 2013. These cases are included in the “Others” section of Table 1.

Comment: Could the authors also discuss why the number of LT has also increased almost double in 2019? Because the donor use rate has also increased? Why has the donor use rate been increasing steadily? Because marginal donor lungs, which were not used previously, have been recently transplanted?

Reply: The donor listing for lung transplantation increased by more than 50% in 2018 to 255 compared to 170 in 2017 and nearly doubled compared to 136 in 2016. This led to longer waiting periods for the patients. Moreover, more than 45% of the total transplant recipients required ventilatory or ECMO support. This led to increased preference for marginal donors, which led to the increase in donor use rate.

Comment: The authors mentioned that the first LDLLT was successfully performed despite the fact that the transplant law by the National Assembly of the Republic of Korea did not allow organ donation from living donor. The case was carefully reviewed and ethically approved by the committee and the institutional review board?

Reply: Thank you for highlighting the concern. The case was carefully reviewed and approved by the IRB of Asan Medical Center. Although LDLLT was not legal in Korea then, it was used as a treatment elsewhere in the world. When performing the LDLLT, Dr Hiroshi Date, Chairman and Professor of Department of Thoracic Surgery, Kyoto University, was invited and he participated in the surgery to successfully perform the transplantation.

Comment: I was very surprised with the fact that almost half of the patients required ECMO or mechanical ventilation support prior to transplantation in Korea. I agree with the authors that such pre-transplant severe condition of recipients is a major reason why the post-transplant outcomes were not so good. As is described in ISHLT guideline, ECLS support before transplant should be recommended or limited to the patients with young age and good potential for rehabilitation. Therefore, they should revise the Korean LAS, discussing not only inclusion but also exclusion criteria for patients with ECLS support.

Reply : Thank you for the comment. We agree that the Korean LAS needs to be revised. The thoracic surgeons who perform lung transplantation in Korea are in consensus that organs should be given to younger patients and those who are expected to have a longer life expectancy ; they have recommended the KONOS to change the LAS guidelines.

Comment: Could the authors show more post-transplant outcomes as possible, such as 30-day mortality, in-hospital mortality, PGD incidence, ECMO requirement rate after transplant, cause of death in the early and late post-transplant period, CLAD incidence, and survival rates sorted by transplant procedure (double vs. single LT), sorted by original diagnosis.

Reply : Thank you for the comment. This study was mainly based on a national registry. The current national registry data does not include such specific results; therefore, it is not possible to provide them in this paper. A further study is thus necessary after the registry is updated with these results.

Minor comments

Comment: Could the authors add when 46.2% of the LT recipients were supported by ECMO or mechanical ventilation in Abstract (p2, line33-34), maybe “prior to transplantation”?

Reply: The phrase “prior to transplantation” has been added in the text.

Comment: please add the unit of waiting period (days?) on Table 3.

Reply: The unit “days” has been added in Table 3.

Comment: Could the authors determine and describe the survival rates and curve by a Kaplan-Meier survival analysis in Figure2?

Reply: The KONOS data provides only the 1,3,5 years post-LT survival. Therefore it is not possible to provide the survival rates using a Kaplan-Meier survival analysis.

Comment: There appear to be a lot of English mistakes, so could the authors ask an English native language expert to check the paper to ensure correctness of the spelling, grammar and syntax?

Reply: The manuscript has been proofread by Editage Online.

Reviewer 2

Comments to the authors:

In this manuscript, the authors review lung transplantation in Korea.

Major Comments:

1. The abstract is too long-winded. It should briefly summarize the data in the article.

Reply: Thank you for the feedback. We have now shortened the abstract by summarizing the data and deleting the AMC data.

2. Much of the introduction is spent discussing humidifier disinfectant ARDS. It can be shortened – how is being pregnant relevant to the discussion? It is also less clear to the reviewer how this event has led to ongoing increases in lung transplantation.

Reply: Thank you for the feedback. Humidifier disinfectant-associated ARDS affected pregnant women more than others because it was believed that the humidifiers helped to maintain an environment favorable for the babies and mothers. Hundreds of cases of humidifier disinfectant-associated ARDS occurred nationwide, and patients requiring LT increased drastically during this period until 2013.

3. What point are you trying to make by introducing LDLLT in the introduction? Why was it done despite it being illegal? Perhaps it should be moved to the discussion or at least after the introduction of KONOS

Reply: Thank you for the feedback. Owing to the Korean LAS, which focuses only on the emergency status of patients, those who are not connected to ECMO or mechanical ventilators rarely receive transplantation. In pediatric patients,

this is more evident because of the lack of donors with matching lung size. LDLLT was introduced to mitigate the lack of donors for these patients. LDLLT was performed after a thorough review and approval by the IRB and intensive study of cases that were performed in other countries. The text describing this information has now been moved to the last paragraph of “History of Lung Transplantation in Korea.”

4. It should be made more clear that it is the pre-transplant rate of support by ventilator or ECMO that is high. Not post-op as it may be interpreted.

Reply: The phrase “prior to transplantation” has been added for better clarity.

5. Some discussion about how organs are allocated between the 5 centers would be interesting.

Reply: KONOS is in-charge of the nationwide distribution of organs from deceased donors. Therefore, when a donor is available, enlisted patients of all centers are listed in a queue based on the emergency status, blood type, and the size of the donor. Priority is given to the first person on the list unless the center passes it to the next patient in line.

6. This article is about lung transplantation in Korea. Why is there such an emphasis on Asan Medical Center? Clearly the authors are from this center, and this bias takes away from the manuscript. Either this bias should be removed, or single center data shown from all 5 centers.

Reply: Thank you for the feedback. All data from 5 centers could not be collected at present. Therefore, the AMC data has been deleted from the paper.

7. Page 8 line 167 sentence isn't finished.

Reply: We have now completed the sentence.

Table 5 should show all zones even if it was 0.

Reply: The table was only partially submitted. The complete table including all zones have been resubmitted.

8. Figure 2 should be a Kaplan Meier survival curve ideally with number at risk and censoring.

Reply: Thank you for the feedback. The reason for showing only the 1-, 3-, and 5-year survival was to show a direct comparison in a single figure. Kaplan–Meier survival curves of both groups cannot be depicted in a single figure.

9. Overall the structure of the manuscript is unusual. Reorganization into a clear introduction, methods, results and discussion sections would help the reader follow the ideas present.

Reply: Thank you for the feedback. The purpose of the study was to review the results of LT published by Korean centers. We chose this structure to introduce the history of LT in Korea, and show the characteristics and results.

Minor comments:

1. Mississippi is spelled wrong

Reply: We have corrected the error.

Reviewer 3

Comments to the authors:

1. The English language should be checked by native speaker.

Reply: The manuscript has been proofread by Editage Online.

2. The authors state that the use ratio of lung donor is comparable to European and North America countries. The survival of recipients in Korea is lower than the data of ISHLT. It is relate to the severity of illness, maybe related to the quality of lung donor. Authors should have a little comment in donor management, such as the introduction of ex-vivo lung perfusion in order to improve the number of donor.

Reply: Thank you for the feedback. Survival of recipients in Korea seems to be lower than that reported in ISHLT because of the severity of the patient's disease at the time of transplantation. Therefore, Korean thoracic surgeons are working together to change the Korean LAS. We did not mention ex-vivo lung perfusion in the paper as the medical insurance system of the Korean government does not allow such expensive treatments to be used at present.

3. The author should insert the mortality of wait-list in the Table3.

Reply: Thank you for the comment. Mortality of patients on the wait list was not provided in the KONOS data; hence, it could not be mentioned in this paper.

4. line208, "donor list" means wait-list?

Reply: The AMC data is excluded and the line deleted.