Author’s response to reviews

Title: Adult lung transplantation case-volume and in-hospital and long-term mortality in Korea

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Author’s response to reviews:

Dear Editor and Reviewers.

First, we would like to express our deep gratitude for your constructive comments that we believe have significantly improved the quality of our manuscript. As we went through the comments and suggestions, we were grateful for the time and effort the reviewers have obviously made to point out important aspects that we had not realized. The following are the point-by-point responses to the reviewers’ comments/questions.

Reviewers Reports:

Reviewer #1

In the manuscript titled "Adult lung transplantation case-volume and in-hospital and long-term mortality in Korea", Dr. Yoon and colleagues insisted that there was no association between case-volume and in-hospital mortality after lung transplantation in Korea. It's a somewhat surprising conclusion when considering it has consistently and reproducibly reported that high volume center shows better results in complicated surgeries.
In-hospital mortality is strikingly high, 32.4% in low-volume center vs. 23.8% in high-volume center, compared with the recently reported 1-year mortality of 16% of ISHLT database. Could you explain the reasons why the early mortality is so high?

> Thank you for your constructive comment and review. As you mentioned, ISHLT recently reported 1-year mortality of 16% within patients who underwent lung transplantation (LT) from 2009 to 2015 [1]. We believe that one of the main reasons for this discrepancy may be the difference in the median case-volume. The centers included in ISHLT report had a median case-volume of 40 LTs per year [1]. However, centers included in our study had a median case-volume of 4 LTs per year and the highest volume centers performed 25 LTs per year. Similarly, Weiss and colleagues showed 1-year mortality of 69.2% and 73.7% in centers with case-volume of 0–2.1 and 2.2–9.4 LTs per year, respectively [2]. Korea is in its early stages in terms of LT with the majority of LTs performed in the past 10 years. Thus, the relatively high in-hospital mortality in our study may not be unique to Korea, rather a phenomenon seen in countries or centers in their initial stage of LT program.

- In discussion section, there is a comment about the relatively poor outcome of the highest case-volume center, and the authors say, 'details would require investigation to understand the reason for the relatively poor outcome'. This comment sounds rather serious. Does the surgeon have any critical problem which needed investigation?

> Thank you for pointing this out. Our description seems to have caused unnecessary confusion. In addition to the surgeon factor, various aspects of patient care should be considered, but was limited due to the retrospective study design. We used ‘investigation’ to imply further evaluation of other aspects of patient care to assess the factors associated with the relatively poor outcome of the highest volume center.

The discussion section (page 9, the 6th paragraph, the 9th sentence) was modified for clarification as follows;

“Detailed clinical assessment of patients who received LT in the highest case-volume center may be required to understand the reason for the relatively poor outcome.”
In Conclusions section, the authors insisted that their 'results may be used as a platform for a discussion on optimal organ distribution for transplantation and improve patient survival after LT'. I could hardly understand how the content of manuscript and the 'optimal organ distribution' are logically related. Is there any problem in organ distribution in Korea?

Thank you for your constructive comment. The Centers for Medicare and Medicaid certification in the US adopted the concept of minimum volume requirements for LT with a volume threshold of ten LTs per year [3]. Therefore, donor organ distribution is directed at those qualified centers.

Improvement of donor utilization is likely to be helpful in Korea due to scarcity of donated organs and the high mortality rate while on the waiting list [4]. However, Korea currently lacks regulation regarding minimum case volume requirements in LT or any other solid organ transplantation program. Although it is controversial whether the case-volume threshold is essential for optimal organ distribution [5, 6], previous studies showed potential benefits of regionalization of LT [2, 7]. Thus, further study based on our report is needed to discuss implications of this type of policy decision.

The conclusion section was revised as follows (Page 10, the first paragraph).

“In conclusion, we were unable to demonstrate an association between case-volume of LT and short- and long-term mortality in Korea. Although our study showed a trend towards improved results in higher volume centers, it seems possible to have favorable outcomes in centers with an annual LT case volume as low as 5. Although a further study with more data would be required for a more definitive conclusion, our results may be used as a platform for a discussion on optimal organ allocation for transplantation and improve patient survival after LT.”

In methods section and in title, it seems that authors have reviewed about the medical cost and long-term mortality, however in results and discussion there is no comments (or not enough comments) on these topics.

Thank you for your insightful comment. Medical cost was one of our secondary outcome when we first planned our study. However, the data for cost from the National Health Insurance Service (NHIS) in Korea only included cost covered by the insurance and not out-of-pocket costs, which can amount to up to 40% of the total cost. Therefore, we decided to exclude the medical cost since it does not reflect the exact cost of LT. We are sorry for the confusion.

The method section was modified as follows:

(Page 5, the 3rd paragraph, the 5th sentence)
“Data on in-hospital mortality, long-term survival, intensive care unit (ICU) and hospital length of stay (LOS) were also extracted.”

(Page 5, the 5th paragraph, the 3rd sentence)

“Other outcomes included ICU and hospital length of stay.”

(Page 5, the 6th paragraph, the 7th sentence)

“ICU length of stay and hospital length of stay according to the case-volume were analysed using the analysis of variance method.”

The result section was modified as follows:

(Page 7, the 5th paragraph, the 1st sentence)

“There were no difference between low- and high-volume centers in other clinical outcomes including ICU and hospital length of stay (Table 4).”

Table 4 has been revised to exclude medical cost.

- The average numbers of each institutions were calculated between 2011 and 2016, however the study period of this manuscript was between 2007 and 2016. Is it right? Is there any reason why the two periods are different?

> Thank you for your valuable comment. In Korea, all of the LTs were done in seven institutions over the last 10 years. The first year when all seven institutions were performing LT was in 2011. Thus, the institutional case-volume was defined as the average number of LTs performed per year between 2011 and 2016.

Reviewer #2:

Dear Author,

The paper is well written but the issue is not enough interesting because of the limitations of your study. The main is that the cut-off and the difference of numbers between high volume and low volume is inadequate to perform a strong statistics. The discussion is potentially interesting but the sense of this paper is poor. As suggestion, you can compare the only really high volume center with the other centers.
Thank you for your constructive and thoughtful review. We agree that the cut-off between low and high volume centers, as well as the difference in case volume, limits a strong statistical analysis. We aimed to see if the effect of LT case volume could be found in Korea, where LT is in its early stages. Only a statistically insignificant trend could be identified, which may not be in accord with previous studies with large number of LTs, but may be used as reference in other countries in their early stages of LT program. The following sentence was added to the third paragraph of the discussion section as follows.

(Page 8, the third paragraph)

“Nevertheless, the trend towards better long-term survival after LT in high volume centers may suggest a potentially positive case-volume effect for regions/countries in early stages of LT.”

We contemplated comparing the one highest volume center with the rest of the centers. However, the comparison, regardless of the result, would not be able to support any conclusion with regards to case-volume because it would be difficult to discriminate whether the difference comes from the high case volume or the characteristics of the one highest case volume center.

Reviewer #3:

It is always interesting see this type of paper which try to look at volume factors in surgery. Certainly the authors have taken on a difficult task by trying to compare low and high volume centers performing lung transplantation.

The problem with this paper is that the number of cases is relatively small and I also find it a bit strange to set the cut-off between high and low volume at 5. This is not a high number according to other publications. The authors claim that there is no difference in mortality and strictly speaking they can say that due to the \( p \) value of 0.052. But that number is really pretty close to significant.

We thank you for your thoughtful comment and meticulous review. All of the previous studies on case-volume and patient mortality in LT have been performed in the United States, with a larger number of patients and a much higher cut-off value of case-volume. As you pointed out, our results were not significant, but did suggest a trend. The significance of our study is that the effect of case-volume associated with better clinical outcome seems to begin in the early stages in healthcare systems where LT is a relatively rare procedure and most institutions have a short history of running the program. The ISHLT report shows that 18% of LT centers have an annual case-volume of less than 10 [1]. Although the majority of centers performing LT are located in Europe (35.2%) or North America (47.6%) [1], more institutions in countries outside of Europe and North America are expected to perform LT in the future. We believe that our results may serve as a guide to countries or healthcare systems where LT is relatively new and also serve as
grounds for regulating LT centers based on their annual case volume. To further elaborate on the potential significance of our results, the following sentence was added to the third paragraph of the discussion section as follows. (Page 8, the third paragraph)

“Nevertheless, the trend towards better long-term survival after LT in high volume centers may suggest a potentially positive case-volume effect for regions/countries in early stages of LT.”

and in the conclusions part as follows. (Page 10, the first paragraph)

“In conclusion, we were unable to demonstrate an association between case-volume of LT and short- and long-term mortality in Korea. Although our study showed a trend towards improved results in higher volume centers, it seems possible to have favorable outcomes in centers with an annual LT case volume as low as 5. Although a further study with more data would be required for a more definitive conclusion, our results may be used as a platform for a discussion on optimal organ allocation for transplantation and improve patient survival after LT.”

Looking at Fig 1 all the centres performing less than 5 have relatively high mortality especially the real low volume centres that have clearly unacceptable results. Two centres with volume just above the cut-off have very low mortality while the center with the largest numbers have a higher mortality about 25%.

I think there are numerous factors potentially unaccounted for that could give more clarity about this number. Such factors may be difficult to get from an administrative database. low volume centres may be very restrictive in the acceptance of recipients, while the bigger players may accept more difficult cases, and they may also accept lungs with longer ischemic time and other unfavorable factors. However, we have no information about this. Without further information about such factors it would be difficult to accept the conclusion made by the authors. Although the issue is still controversial, it seems documented for a number of procedures that higher volume gives better results, everything else being equal.

It seems to me that the conclusion of this study would be that there is a trend towards improved results in higher volume centers, but that it is possible to have good results in centres with low volume as low as 5. Centres with very low numbers have unacceptable results.

> Thank you for your constructive review and comments. We looked through our data to see if any clinical information available were not accounted for, but were unable to recover any additional data. The regression analysis using the limited and restricted data did account for baseline characteristics such as age, sex, diagnosis, and underlying disease. As you pointed out, we agree that the initial conclusion stated by the authors were not fully supported by the data and therefore was modified as follows to reflect the results more appropriately.

(Page 10, the first paragraph)
“In conclusion, we were unable to demonstrate an association between case-volume of LT and short- and long-term mortality in Korea. Although our study showed a trend towards improved results in higher volume centers, it seems possible to have favorable outcomes in centers with an annual LT case volume as low as 5. Although a further study with more data would be required for a more definitive conclusion, our results may be used as a platform for a discussion on optimal organ allocation for transplantation and improve patient survival after LT.”

Are the authors of this article working in one of the hospitals performing lung transplants? In that case I believe this should be mentioned as a possible conflict of interest.

> Thank you for your insightful comment. The authors of this article are working in one of the centers performing more than 5 LTs per year. We added it in the Competing interests section as follows:

(Page 12, Competing interests)

“The authors of this article are working in one of the high-volume centers performing more than 5 LTs per year. Otherwise, the authors declare no competing interests.”

In addition to the revisions in response to your constructive review and valuable comments, we added a few references in our manuscript to provide more information to the readers as follows:

(Page 14, 16, 17)


I would like to thank the editors and the reviewers once again for their constructive comments and suggestions. I feel that by revising our paper according to the suggestions by the reviewers, the quality of our manuscript has improved significantly.
Sincerely,

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References


