

Peer Review File

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Review Comments

Reviewer A: Thank you very much for the insightful comments, which were very helpful to improve the study. Please see our response following.

Comment 1: For me, this raises the question of whether this makes sense for economic and process reasons. I would expect this reference at least in the limitations. This is especially true against the background of increasing cost pressure. Furthermore, I assume that critical patients who are urgently listed are primarily treated in high-volume clinics. Please clarify.

Answer 1: In Japan, qualified medical personnel perform lung transplantations in addition to routine lung cancer surgery and there is usually no special team designated for lung transplantation. Facilities with a high number of lung transplants have full-time coordinating nursing staff, while nursing staff at facilities with a low number of lung transplants perform coordination for lung transplantation cases in addition to their regular nursing duties. For that reason, there is no cost incurred to maintain the lung transplant system. In addition, under the Japanese allocation system, transplants are allocated in the order of registration, thus there is no relationship between severity of illness and allocation of transplants.

Changes 1: The following has been added to the Discussion section in the revised manuscript. “In Japan, qualified medical personnel perform lung transplantations in addition to routine lung cancer surgery and there is usually no special team designated for lung transplantation.”

Reviewer B: Thank you very much for the insightful comments and questions, which were very helpful to improve the study. Please see our responses following.

Comment 1: With organ transplant laws in Japan being amended in July 2010, allowing families to consent to organ donation, how do the authors see this paradigm shift influencing lung transplant volume in Japan?

Answer 1: As noted by the reviewer, the number of lung transplants has been on the rise following revision of the law. Furthermore, that number has increased markedly in the past 1-2 years, and there appears to be recent changes regarding the view of life and death in Japanese society. Since this study is intended to be a summary of the past two decades, we did not separately evaluate that recent time period for this review.

Changes 1: No changes.

Comment 2: How many of these transplants were performed in the last decade?

Although not a primary object of the study, I think it would be good to state that number to see if the above laws have had an impact on volumes in Japan.

Answer 2: This study was conducted using data with personal information removed, thus the date of surgery was not available and data from the last 10 years could not be examined. Nevertheless, since the number of transplants has increased after revision of the law, it will be necessary to examine trends in the decade following this study, which summarizes total transplants in Japan from 2000 to 2021.

Changes 2: The following sentence has been added to the revised Discussion section. "It will be necessary to examine trends in the decade following this study, which summarizes results of all transplantations performed in Japan from 2000 to 2021, as the number of LTs is increasing following revision of the organ transplant law."

Comment 3: The obvious danger for a very low-volume program would be that one or two bad outcomes may adversely affect the perception of quality of care.

Answer 3: As the reviewer pointed out, one death in a facility with a small number of transplants can significantly increase the mortality rate. Such facilities may opt for single-lung transplantation, which has a lower perioperative mortality rate. In fact, low volume centers included in the present showed a high proportion of single-lung transplantation.

Changes 3: The following sentences have been added to the revised Discussion section. "A higher rate of single LT procedures was observed in the LV group. It is considered

that centers dealing with a limited number of patients might opt for single LT, which is expected to have shorter operation times and lower perioperative complications.”

Reviewer C: We sincerely appreciate the insightful comments and suggestions, which were very helpful to improve the study. Please see our responses following.

Comment 1: It may be interesting to describe some details of the accreditation process in Japan. What’s necessary to accreditation? That information would be of great value to foreigner institutions that seek for great results in lung transplant.

Answer 1: The requirements for accreditation in Japan are diverse and include number of usual thoracic surgeries performed, experience with bronchoplasty and angioplasty in lung cancer cases, number of publications related to lung transplantation, and qualifications of the anesthesiologists and paramedical staff members, along with several others.

Changes 1: The following sentence has been added to the Discussion section in the revised manuscript. “The requirements for accreditation in Japan are diverse and include number of usual thoracic surgeries performed, experience with bronchoplasty and angioplasty in lung cancer cases, number of publications related to lung transplantation, and qualifications of the anesthesiologists and paramedical staff members, along with several others.

Comment 2: The paper describes the institutional volume, however it’s not clear for the reader the team expertise. Should we believe that the low volume

institutions have less experienced surgeons and multidisciplinary team members? It's not rare that experienced professional change jobs from high volume centers and stars in low volume ones. It may be interesting to analyze the results by number of procedures performed by surgery team as well.

Answer 2: In Japan, transplant teams rarely move between facilities. However, each team often has several members who have experience in other countries.

Unfortunately, data regarding number of transplants per surgeon were not available in the database.

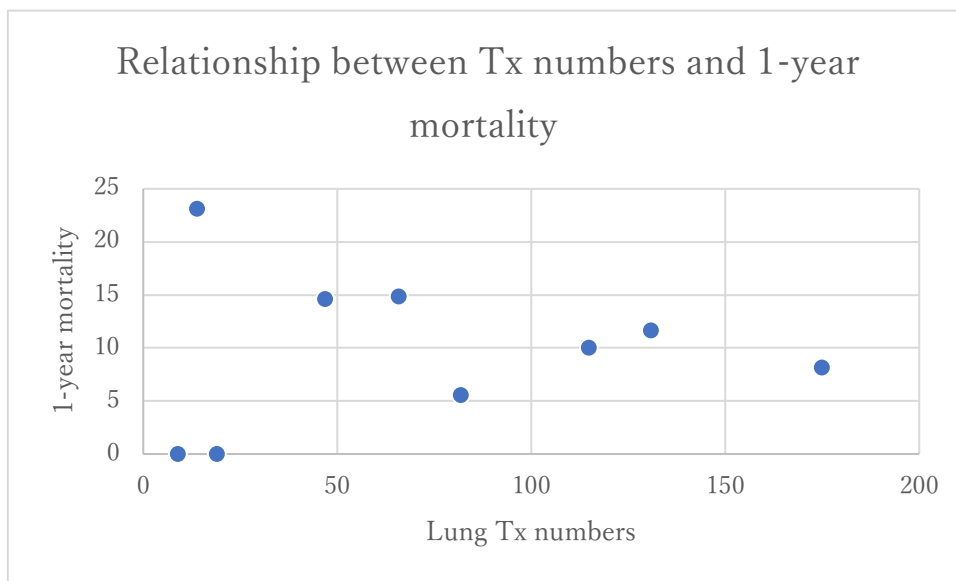
Changes 2: No changes.

Reviewer D: Thank you very much for the insightful comments, which were very helpful to improve the study. Please see our response following.

Comment 1: The authors should be encouraged to explore the C statics of volume to define and quantitate this explicitly. Also, the authors should identify what other factors contribute in this manner. They should also provide data on PGD levels.

Answer 1: For cases in Japan, it is difficult to calculate the cutoff value using C statistics, because no correlation was found between number of transplants and mortality rate among institutions, as shown in the figure below. If such a correlation was found, then it may be useful to calculate the area under the ROC curve to obtain

an appropriate cutoff value. Although we were unable to find factors affecting mortality, the results obtained showed that the low number of transplants is an important factor related to the variations between centers. It is unfortunate that there were no PGD-level data available in the database.



Changes 1: No changes.

Reviewer E: Thank you very much for the insightful comments, which were very helpful to improve the study. Please see our responses following.

Comment 1: Please elaborate (with references if possible) on why the cutoff of 8 was chosen.

Answer 1: Since the number of lung transplants in Japan is quite low as compared to other countries, it was difficult to select an appropriate cutoff value for comparisons

among Japanese institutions from previous reports. Therefore, we prepared Figure 1, which shows a reasonable difference between the high- and low-volume centers.

Changes 1: No changes.

Comment 2: The formula provided for mortality calculation is somewhat confusing. Please clarify it in a better way.

Answer 2: The text has been edited for better clarity.

Changes 2: “(number of patients died within period) / (number of patients died during period + number of patients survived beyond period)”

Comment 3: Please provide more information in table 1, especially relating to disease, as the “others” is almost half of both groups.

Answer 3: LAM and COPD have been added to Table 1. Now, “Others” is less than 30%.

Changes 3: Table 1 has been revised.

Comment 4: Please provide more details about figure 3. Any statistical tests? What is the utility of having these plots. Since centers can not be identified, how should the reader contextualize these plots?

Answer 4: We have added more detailed information regarding the centers to the legend of Figure 3. Log-rank testing was conducted using a SPSS statistics software program.

Changes 4: Some related changes have been made the figure legend.

Comment 5: Please tabulate all survival data.

Answer 5: A table showing survival data was created.

Changes 5: Table 2 has been added to the revised manuscript.

Comment 6: Do the authors think continuous non-linear analysis of case volume and survival would be more informative in addition to the stratified analysis?

Answer 6: For the present study, we performed a stratified analysis based on case volume, as case volume and survival were not linear. On the other hand, we did not conduct logistic regression analysis for factors related to lung transplantation, because we wanted to elucidate the disparity between type of facility.

Changes 6: No changes.

Comment 7: Since authors assert that perioperative management could be reason for good outcomes, what measures of perioperative management can they present in support of it? Is there any data on this?

Answer 7: Since this study was conducted using a database that did not include data regarding perioperative management, there were no data available to provide a measure of perioperative management for good outcomes. Why outcomes for LT at institutions in Japan are better remains a mystery. Furthermore, not only are LT outcomes better, but lung cancer surgery outcomes overall are also better as compared to other countries. Something is responsible for these findings, but we could not address that in this study because of the limitations of the database.

Changes 7: The following sentence has been added to the revised Discussion section. "This study was conducted using a database that did not include data related to perioperative management, thus none were available to examine the effects of perioperative management for good outcomes."

Comment 8: What are the possible reasons for outcomes variability in LV centers?

Answer 8: In the HV centers, performance was stable and good, while that in the LV centers was uneven. As several other papers have pointed out, inexperience in LV centers can lead to poor results, though a good team, when organized, seems able to achieve good results even with a small number of LTs.

Changes 8: The following sentence has been added to the revised Discussion. “As several papers have pointed out, inexperience in LV centers can lead to poor results, though a good team, when organized, seems able to achieve good results even with a small number of LTs.”

Comment 9: Do the authors think there were no differences in outcomes because the volume of transplants was not large enough to show any such effect? As can be seen, the KM does hint at a trend for better survival in HV centers. Please discuss in detail.

Answer 9: Results obtained at the HV centers were stable. It is expected that as the number of transplants performed at LV centers increases, the results of the poorer performing centers will improve, while the better performing centers will decline due to the appearance of death cases, and the results will eventually converge.

Changes 9: The following sentences have been added to the revised Discussion section. “The average survival rate for the LV group was much better than that reported by the ISHLT and the results obtained at the HV centers showed stability. It is expected that with an increased number of transplants performed at LV centers the results of those with poor performance will improve. Such an increase at those centers will likely lead to a decline in results at the better performing centers due to the appearance of death cases, and the results will eventually converge.”