

Peer Review File

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Reviewer A

Comments to the authors:

This is a review article describing the history and current practice of lung organ donation and transplantation in Japan, highlighting the unique culture and legislative features in Japan and the associated problems and challenges. The author also described and how the author's team (or other lung transplant workers) attempted to overcome the challenges of donor shortage and the outcome of lung transplant cases in Japan in terms of survival.

This review is an invited article in the series on lung transplantation and I have to thank the journal for providing this platform for sharing of knowledge, experience and practice among different Asian lung transplant centres. I enjoyed reading this article and have to congratulate the Japanese colleagues on their very good work and results in lung transplant. I am sure there would be a lot that we can learn from them.

As for a critical review of the submitted manuscript, the followings are my queries, comments and suggestions:

Comment 1: On the structure of lung transplant programmes in Japan, are they run by solely thoracic surgeons. Are respiratory physicians involved in the assessment of potential recipients and the follow up care of the post-transplant patients? There are nine lung transplant centres in Japan. Are all centres being run in the same way or are there any difference in practice?

Reply 1: Not all centers are run in the same way, but nine LTx programs are mainly run by thoracic surgeons.

Comment 2: As Japan is not a small country, what is the usual follow up practice for lung transplant patients? Are they being followed up in the lung transplant centres or being referred to other centres for follow up?

Reply 2: Post-op follow-up care are also mainly done by thoracic surgeons at the LTx centers where the patient underwent LTx. In case the patient lives far away from the

center, the patient is referred to a respirologist or thoracic surgeon close to the patient home.

Comment 3: There were nine lung transplant centres in Japan. Are the case volume similar among the nine centres?

Reply 3: No, activity is variable.

Comment 4: On the assessment of potential recipients, what were the criteria being used for being accepted for “registration” for lung transplant?

Reply 4: The criteria are below

1. The patient must be under 60 years of age for unilateral lung transplant and under 55 years of age for bilateral lung transplant.
2. The patient must have a poor prognosis.
3. The patient must have no other life-threatening systemic disease.
4. The patient must have demonstrated absolute compliance with medications and medical recommendations, and have good rehabilitation potential.
5. The patient must demonstrate emotional stability.
6. The patient must have a supportive person or supportive social system

Comment 5: Line 76: Please clarify the lung organ donor allocation system in Japan. Do you mean with matching in blood group and lung size, the recipient waiting time on the waiting list was the only criteria for allocation?

Reply 5: Yes, we do.

Comment 6: If that was the case of lung organ allocation, would there be a situation of very early referral and registration for patients in Japan in order to gain “waiting time”?

Reply 6: Yes, exactly, sometimes it happens. We have added the description about it. However, as the number of patients awaiting LTx increases, the assessment has been getting strict.

Comment 7: Line 82: did the author think that the lung donor allocation system was a “fair” one? From medical point of view, do the authors believe this was a good system?

Reply 7: I think it is fair, but it is my personal opinion. I deleted the sentence.

Comment 8: Line 136: the authors mentioned a few strategies that helped to increase

the numbers of lung transplants. May I know whether this was the practice of the author's own centre, or the standard practice across all transplant centres in Japan? Was there any data that such practice improved the lung transplant number and outcome?

Reply 8: This practice is standard across all transplant centers.

Comment 9: Line 171: scientifically speaking, the use of ECMO in support of patients awaiting lung transplant would not affect the lung transplant numbers, but only improve the wait-list mortality, as the number of patients on waiting list is much bigger than the supply of donor organs.

Reply 9: Exactly. I added your point to our main text.

Comment 10: On living-donor lung transplants, Japan is a world-renowned country for the excellent skills, experience and patient outcome with living-donor lung transplant. I think most readers would be very interested to know more about the practice of living-donor lung transplant and the key factors for the very good results.

Reply 10: Several references about living-donor LTx were added for details. We are not sure yet why our results are good.

Comment 11: Was there any data about the outcome (mortality and morbidity) of the living-lung donors?

Reply 11: There has been no reported perioperative mortality of a lung donor. The percentage of intra- or perioperative complications has not been well documented. Reported complications of lung donors are the necessity of a right middle lobe sacrifice, pericarditis, and accumulation of pleural effusion which needed chest tube drainage.

Comment 12: Line 221: I was very impressed by the very good outcome in terms of survival, especially as mentioned in the paper that they were using many marginal donors and there was no recipient selection (organ allocation just by the recipient's order on the waiting list). Is the immunosuppression and anti-infective practice for lung transplant similar to those in western countries? Were the survival figures similar across all lung transplant centres in Japan? Could the author offer any reason(s) for their very good outcome?

Reply 12: Practice for LTx is quite similar to those in western countries. We are not sure why the results are good in Japan.

Comment 13: Lastly, I would suggest the authors doing a revision in the quality of English of the manuscript. Some of the terms being used were not correct in expressing what the authors were trying to say, for example, “we challenge the shortage of organ donors”. The correct way to express the meaning could be “we overcome the challenge of donor organ shortage”

Reply 13: If it is needed, we will submit the certificate of English proof.

Reviewer B

Comments to the authors:

The reviewer is honored to review this review article about lung transplantation in Japan. The article is simple, but well written and easy to understand for the readers all over the world. There are several points to be revised, as follows:

Comment 1: On Line 23, the number of lung transplantation was cited from the Registry data, which required the reference (1).

Reply 1: Line 23 is in the abstract, so we did not put the ref#.

Comment 2: On line 29, the reviewer strongly recommend that the authors should cite the Hoshikawa’s paper which described the effect of Japanese medical consultant system.

Ref. a1) Hoshikawa Y. Okada Y. Ashikari J. et al. Medical consultant system for improving lung transplantation opportunities and outcomes in Japan. *Transplant Proc.* 2015 Apr;47(3):746-50.

Reply 2: Thank you. Line 29 is in the abstract. We added the reference to the main text.

Comment 3: On line 73-75, the reviewer could not understand the meaning of this example. If the authors want to show the complex system in Japan, more precise example might be chosen.

Reply 3: We edited the description.

Comment 4: On line 139, the authors might cite the paper shown above (Ref.a1)

Reply 4: Corrected

Comment 5: On line 158-160, “X-ray” should be “roentgenography”.

Reply 5: We changed X-ray to radiographs.

Comment 6: On line 170, if the authors need an evidence from Japan, Kayawake’s paper would be appropriate in this context.

Ref. a2) Kayawake H, Chen-Yoshikawa TF, Aoyama A, et al. Surgical management of bronchial stumps in lobar lung transplantation. J Thorac Cardiovasc Surg. 2018 Jul;156(1):451-460.

Reply 6: We added the ref.

Comment 7: On line 197, the reviewer recommends that the authors should add the word, such as “basically” and “generally” because the criteria of a living-donor LTx is different among the LTx centers in Japan. Some centers ok with the age of 60 and others do not accept third degree of relatives.

Reply 7: Thank you for pointing it out. We added the word.

Comment 8: On line 205 and others, “post-bone marrow transplant lung disease” must be revised as “pulmonary complications after hematopoietic stem cell transplantation (HSCT)” or “post-hematopoietic stem cell transplant lung disease”.

Reply 8: We changed it to “post-hematopoietic stem cell transplant lung disease”.

Comment 9: On line 214, inverted right to left living-donor LTx is also a useful option for overcoming a small-for-size graft, which was also developed in Kyoto. Please add the most recent paper published in Eur J Cardiovasc Surg by Chen-Yoshikawa et al.

Reply 9: We added it. Thank you.

Reviewer C

Comments to the authors:

This article unveils the difficulties and challenges of lung transplantation in Japan in particular on the scarcity of donors and their adaptations in overcoming these challenges. I would also like to congratulate the authors on the high survival rate of lung transplant patients including the NDD and living-donor LTx in Japan.

I think the readers are interested to know more about the details on the followings.

Comment 1: Quality of marginal donors like the age distribution, contralateral pneumonia rate, duration of intubation, etc and the retrieval rate of donor lungs.

Reply 1: We are not allowed to access all donor data which are stored in the Japanese Organ Transplant Network, therefore, it is hard to know the age distribution, contralateral pneumonia rate and duration of intubation. The retrieval rate of donor lungs was mentioned in the Date's paper. It was 60%.

Comment 2: Despite that the system of allocation of recipient is a "first-come-first serve" basis, IIP plus other IP still constitute a significant proportion of bilateral NDD transplants. Is that these patients were not selected for single lung transplant because of their blood type, extreme size or other factors that they need to wait for the double lung transplant round and when time goes by, pulmonary hypertension developed while on waiting that they were only eligible for double lung transplant? Or are there other factors that could explain the relatively high proportion of these patients in bilateral NDD than unilateral NDD transplant?

Reply 2: Pulmonary hypertension and the existence of chronic pulmonary infection such as non-tuberculosis mycobacteria and fungi are major reasons for bilateral LTx.

Comment 3: Line 133: Bilateral lung transplant may be necessary for IIP patients with pulmonary hypertension at the time of unilateral LTx. What is the logistics in the preparation of the second recipient planned to receive the other side of lung of the same donor?

Reply 3: It is only based on the waiting list. Donor lungs often go to two different LTx centres.

Comment 4: The outcome in particular the 5-year survival rate is superior to the international average in spite of the use of marginal donors and the high proportion of technically demanding PAH recipients. What are the possible reasons of the high survival rate? Is the infection rate particularly low? Did the PAH patients experience complicated post-operative course? What is the rate of multi-organ failure and what is the length of ICU stay for this particular challenging group of patients?

Reply 4: PAH patients have more complicated post-operative course than other LTx recipients. Post-op bleeding rate which needs re-operation is higher in PAH patients. We in Tokyo use post-op VA ECMO for all cases of PAH. Multi-organ failure rate is

not high, but we do not have detailed data.

Reviewer D

Comments to the authors:

Comment 1: What will you do if you first observe the secondary PAH through Swan-Ganz catheter during the time of unilateral LTx?

Reply 1: Nothing we can do for it. We just continue to do unilateral LTx. Long-term prognosis was not good. Based on the experiences, we are getting more careful to monitor PA pressure during the long waiting time.

Comment 2: The Japanese lung transplantation groups have achieved a great outcome in living-donor lung transplantation. Can you state the mortality and morbidity of donor after surgery?

Reply 2: Mortality is zero. We do not have data about morbidity.

Comment 3: Although the living donor lung should be better than any brain-dead donor lung, the long-term survival is comparable between the living-donor lung transplantation and NDD lung transplantation. The authors should have a little comment about it.

Reply 3: Thank you for pointing it out. Size-mismatch in living-donor LTx might be one explanation for lowering its survival rate.

Reviewer E

Comments to the authors:

Comment 1: This article includes the review of clinical cases of living donor lung transplantation. Please confirm if the ethical approval was obtained and include this information in the text.

Reply 1: We have obtained written consent from all patients.