

Review Comments

Reviewer A:

Thank you for the opportunity to review this interesting review paper from the Okayama group where the first successful living donor lobar lung transplant in Japan was performed. This manuscript gave a very detailed description of the important chronic complications after lung transplant and the authors provided useful insights into the unique Japanese experience- (1) the fact that LDLLT accounts for almost 30% of the total number of lung transplants, as well as the much higher percentage of single lung transplant; (2) the excellent survival outcomes after lung transplant, be it cadaveric or LDLLT. The readers of JTD would find this review very interesting. I would suggest the following to make this review even more informative:

Comment 1: lines 117-121

Regarding the use of perfusion scintigraphy to detect early signs of CLAD in LDLLT, please consider providing some images to illustrate this shift of perfusion to the contralateral unaffected lung that the authors described in this section. Most lung transplant clinicians outside of Japan would not have much first hand experience with LDLLT, so a few pertinent illustrations here would be very useful.

I note that this same group recently published a paper on this subject where the manuscript contained some nice images. [Sci Rep. 2020 Jun 29;10(1):10595. doi: 10.1038/s41598-020-67433-4.]

Reply 1: We would like to thank the constructive comment. We added a figure of lung perfusion scintigraphy as the new Figure 1 showing unilateral CLAD after LDLLT.

Change in the text: We added the legend of the new Figure 1 as follows (line 351), “Representative image of unilateral chronic lung allograft dysfunction (CLAD) after bilateral living-donor lobar lung transplantation. Lung perfusion scintigraphy demonstrates a perfusion shift to the left unaffected lung in a patient with right unilateral CLAD.”

Comment 2: In addition to the overall survival in Figure 1, the authors can consider adding another figure showing CLAD-free survival in Japan after lung transplant.

Thank you once again for the chance to review this interesting manuscript.

Reply 2: Unfortunately, there is no figure available of CLAD-free survival using the national data in Japan. I apologize that we cannot add the figure of CLAD-free survival in Japan that the reviewer suggested.

Change in the text: No change.

Reviewer B:

Dear authors

the presented paper is a review article on current management of patient undergoing lung transplant rather than presenting new data. As presumed that lung transplant is rarely done in

Japan it contains interesting data concerning incidence and treatment option of various post transplant disorders.

Comment 1: Presenting own data in tables would make it easier to follow the written text and can shorten some passages. Comparison of ISHLT data would be interesting.

Reply 1: According to the reviewer's suggestion, we described the comparison of the ISHLT data with the Japanese data.

Change in the text: We added the following sentence in the part of long-term survival (line 324), "The survival rate after LT in Japan appears to be better than that of the registry report from the ISHLT despite the limited number of LT in Japan."

Comment 2: Concerning table 1 there should be pointed on the different graphs 1 A and 1 B.

Reply 2: As the reviewer suggested, we added a new figure showing the number of single and bilateral CLT and LDLLT as well as overall survival after LT in Japan as the new Figure 2.

Change in the text: We added the legend of the new Figure 2 as follows (line 355), "Figure 2. Overall survival after cadaveric lung transplantation (CLT) (n = 658), living-donor lobar lung transplantation (LDLLT) (n = 270) and heart-lung transplantation (n = 3) in Japan (A). The 5-year and 10-year overall survival rates were 73.72% and 61.37% after CLT, 73.84% and 62.48% after LDLLT, respectively. The 5-year overall survival was 75.69% after bilateral CLT (308 patients), 71.84% after single CLT (350 patients), 74.53% after bilateral LDLLT (227 patients), and 69.96% after single LDLLT (43 patients) (B). This figure was reproduced from reference (2) with permission from the Japanese Society of Lung and Heart-Lung Transplantation."

Comment 3: Data of 1 A that reveal a much better outcome after a single the bilateral lung transplant which doesn't reflect the international data. This should be explained in the text.

Reply 3: This is because this special issue "Why is the outcome good? Secrets of lung transplantation in Japan" is proposed in JTD. Many factors, including pre-, intra-, and post-transplant factors, seem to affect a better outcome of LT in Japan, and presumable factors are discussed in each review of this special issue.

Change in the text: No change.

Comment 4: To complete it would be helpful to address your routine immunosuppressive management and whether you use induction mAB and also in managing acute allograft rejection.

Reply 4: Since we are required to describe the long-term management after LT in this review article, we would appreciate it if the reviewer could understand that the routine immunosuppressive management is discussed in the other review article of this special issue "Why is the outcome good? Secrets of lung transplantation in Japan."

Change in the text: No change.

Comment 5: Shorten the explanation of CLAD and rely to ISHLT criteria

Otherwise, it is a clear and understandable written report that I can recommend of publication after minor revisions. Best regards

Reply 5: As the reviewer suggested, we shortened the explanation of CLAD and the ISHLT criteria.

Change in the text: The following sentences and phrases were removed, “Long-term survival after LT remains worse than that after other solid organ transplantation (line 78)” “with a fall in FEV1 to <80% of the baseline value (line 88)” “; undefined CLAD refers to patients who do not meet the current definitions of BOS, RAS, or mixed phenotypes (line 91).”

Reviewer C:

I read this review paper with great interest that highlights the long-term survival as well as unique posttransplant management after lung transplantation in Japan.

First of all, their long-term survival data with 73% at 5-year and 61-62% at 10-year for both cadaveric and living-related lung transplantation are so impressive that all the teams involved in those patients' care should be congratulated for such outstanding success. It's easy to attribute it to their identical ethnic backgrounds between the donor and the recipient; however, I believe that their dedicated, high acuity care supported by the solid social insurance system in Japan would contribute to their excellent long-term outcomes. That being said, from the currently presented data alone, it remains to be completely clarified regarding what has most driven such good long-term outcomes after lung transplantation.

Comment 1: Can the authors demonstrate their data for hospital readmission (incidence, count, cumulative duration, reasons for) after lung transplantation to see if it may contribute to transforming their trajectory?

Reply 1: Unfortunately, we don't have any data for hospital readmission, but we are sure that almost all the patients required hospital readmission in our hospital, because the health insurance system in Japan covers the admission fee when the patients develop any diseases, including pneumonia, CMV infection, and enteritis, etc. We would like to examine the cumulative duration or reason for hospital readmission in the future research.

Change in the text: No change.

The previous literatures report that hospital readmission after lung transplantation negatively affects quality of life and resources utilization; however, given the unique circumstances in Japan regarding health care system and resources as reported elsewhere, in particular in the sense that the surgeons provide high acuity care to the patients for their post-transplant management due to limited availability of pulmonary transplant specialists, there may be underdiscussed reasons in such data that can better explain the successful outcomes in Japan. In North America, despite known, notable complexities inherent to the nature of lung transplantation, the patients' post-discharge care is somewhat affected and limited by the health care resources and often become compromised, leading to their suboptimal outcomes.

Comment 2: If the group demonstrates the granular dataset of their patients' readmission and patient-centered post-discharge care that would lead to excellent posttransplant long-term outcomes, it will be a new and great message to the worldwide lung transplant community. Thank you for this privilege.

Reply 2: Unfortunately, we don't have any datasets of the patients' readmission after LT in our hospital. Since almost all the patients in our hospital experienced hospital readmission owing to

the health insurance coverage in Japan, we would like to investigate the rate and frequency of hospital readmission in the future research.

Change in the text: No change.

Reviewer D:

This is an interesting and carefully prepared study describing specificity of LTx program in Japan caused predominantly by legal regulations and restrictions (high number of cadaveric donors and living lobar donors as well as for example lack of coverage of sirolimus or everolimus after LTx by Japan health insurance program). This paper is to some extent review of Japan experience with complications treatment than scientific analysis. Its major value for the readers is based on specificity of Ltx programs in Japan in comparison to other countries.

Comment 1: I would like to ask authors to add an information regarding early postoperative mortality. Some minor language errors should be corrected as well.

Reply 1: Because we are required to describe the long-term management after LT in this review article, we would appreciate it if the reviewer could understand that early postoperative mortality is discussed in the other review article of this special issue “Why is the outcome good? Secrets of lung transplantation in Japan.”

Change in the text: No change.

Reviewer E:

The reviewer is honored to review a review article about long-term management and outcome of lung transplantation in Japan. The paper itself is well written and its contents are very educative, but there are still several points to be revised as follows:

Comment 1: The journal is an international journal written in English, and so the references should be written in English. Please delete the paper written in Japanese, such as Ref 38 and 78.

Reply 1: As the reviewer suggested, we deleted the Japanese title of the new Ref 37 and 84.

Change in the text: The following titles were removed, “Noushi katahai ishoku no chouki seiseki” in Ref 37 (line 490) and “Haiishoku go no manseijinzoubyou ni taishite ketsuekitouseki o dounyuushita syourei no kentou. Ishoku” in the new Ref 84 (the former Ref 78 (line 598).

Comment 2: As the authors showed in the title of this paper, it would be better for the authors should cite more papers from Japanese lung transplant institutions written in English. The reviewer believes there would be more interesting papers in this field of lung transplantation reported by Japanese lung transplant centers. Regarding malignancy, the reviewer suggests citing a paper written by Tanaka et al. (PMID 26983711)

Reply 2: We added a paper written by Tanaka et al. (PMID 26983711).

Change in the text: Ref 46 was newly added (line 175, 509).

Comment 3: In CMV infection, the reviewer suggests citing a paper written by Ohata et al. (PMID 29049752), and Koshizuka et al. (PMID 30552996). GCV resistant CMV infection might be an important topic.

Reply 3: We added a paper written by Ohata et al. (PMID 29049752) as an experience of CMV management in Japan. We described only the essence of CMV management in this review, and a paper written by Koshizuka et al. (PMID 30552996) seems to be a little different from the description of our review. So, we did not add this paper in the reference.

Change in the text: Ref 70 was newly added (line 249, 563).

Comment 4: In Aspergillus infection, the reviewer suggests citing a paper written by Tachibana et al. (PMID 29773296), Kato et al. (PMID 24593162), and Katada et al. (PMID 34649759). Especially, the article written by Tachibana et al would be important in that this is the first multicenter study of nontuberculous mycobacteria and/or Aspergillus infections in lung transplant recipients in Japan (Fujita et al. PMID 29773288).

Reply 4: We added papers written by Tachibana et al. (PMID 29773296) and Katada et al. (PMID 34649759) as the new references. A paper of Kato et al. (PMID 24593162) was published from the same institution of Katada's paper, and the updated data seemed to be included in the Katada's paper.

Change in the text: Ref 60 (line 228, 540) and 61 (line 229, 542) were newly added.

Comment 5: Regarding COVID-19 infection, the authors should cite a paper by Goda et al. (PMID 36289168).

Reply 5: In addition to a paper by Goda et al. (PMID 36289168), we added a paper of COVID-19 vaccination written by Hirama et al, which included 41 recipients of LT.

Change in the text: Ref 71 (line 257, 565) and 72 (line 257, 567) were newly added.

Comment 6: In CKD, the authors should cite a paper by Katahira et al. (PMID 33062846).

Reply 6: We added papers written by Katahira et al. (PMID 33062846)

Change in the text: Ref 83 was newly added (line 293, 595).

Comment 7: Conclusions seemed to be too long. Please shorten the conclusion.

Reply 7: We shortened the conclusion as below.

Change in the text: In accordance with the reviewer's comment, the following sentences were removed, "Because PTLN is the most common malignancy after LT (line 336)."

Reviewer F:

I was honoured to have the opportunity to review the manuscript by Seiichiro Sugimoto and colleagues entitled "Long-term management and outcome of lung transplantation in Japan". This is an interesting review dealing with the most important problems regarding the long-term management of lung transplant recipients (CLAD, malignancies, infections, and chronic kidney disease), especially focused to the Japanese population.

In general, the manuscript is clearly written and interesting for the readers. I would recommend some minor changes and the inclusion of specific comments as outlined as follows:

Comment 1: Rates of SCLT and LDLLT are higher in Japan. May the authors comment on the reasons for these differences?

Reply 1: To overcome the extreme donor shortage, SCLT and LDLLT are performed more frequently in Japan than in the world. We would appreciate it if you could find the following sentence in the Introduction, “In contrast, compared with bilateral CLT (33.1%, 308 patients), the rate of single CLT (37.6%, 350 patients) and LDLLT (29.0%, 270 patients) are relatively high in Japan because of the extreme donor shortage.”

Change in the text: No change.

Comment 2: May the authors include information regarding the indications for lung transplantation and their corresponding type of procedure performed?

Reply 2: Since we are required to describe only the long-term management after LT in this review article, we would appreciate it if the reviewer could understand that the indications for lung transplantation and their corresponding type of procedure performed are discussed in the other review article of this special issue “Why is the outcome good? Secrets of lung transplantation in Japan.”

Change in the text: No change.

Comment 3: May the authors include survival by indications and survival of re-transplants?

Reply 3: Indications for lung re-transplantation are discussed in the other review article of this special issue “Why is the outcome good? Secrets of lung transplantation in Japan.” Survival of re-transplantation is similar to that of initial lung transplantation in our hospital. But we did not include survival of re-transplantation in this review due to the small number of re-transplantation.

Change in the text: No change.

Comment 4: Figures refer to one hospital. What about the rest of 9 transplant centers? May the authors include survival from their National Registry?

Reply 4: According to the reviewer’s suggestion, we added the survival of lung transplantation from the National Registry in Japan as a new Figure 2.

Change in the text: We added the legend of the new Figure 2 as follows (line 355), “Figure 2. Overall survival after cadaveric lung transplantation (CLT) (n = 658), living-donor lobar lung transplantation (LDLLT) (n = 270) and heart-lung transplantation (n = 3) in Japan (A). The 5-year and 10-year overall survival rates were 73.72% and 61.37% after CLT, 73.84% and 62.48% after LDLLT, respectively. The 5-year overall survival was 75.69% after bilateral CLT (308 patients), 71.84% after single CLT (350 patients), 74.53% after bilateral LDLLT (227 patients), and 69.96% after single LDLLT (43 patients) (B). This figure was reproduced from reference (2) with permission from the Japanese Society of Lung and Heart-Lung Transplantation.”

Comment 5: May the authors include information regarding two cases receiving a SCLT + LDLLT? Which is the rationale for such an exceptional procedure?

Reply 5: Indication for SCLT + LDLLT, which is called “hybrid lung transplantation,” is discussed in the other review article of this special issue “Why is the outcome good? Secrets of lung transplantation in Japan.” We would appreciate it if you could find the detailed information of hybrid lung transplantation in Ref 87. (Kurosaki T, et al. "Hybrid Lung Transplantation" Combining Living Donor and Cadaveric Lung Transplants: Report of 2 Cases. *Transplant Proc*

2021;53:2004-2007.)

Change in the text: No change.

Comment 6: The authors stated in the abstract “the similar survival outcomes of single CLT and LDLLT, compared with bilateral CLT, might contribute to improved long-term survival in Japan”. This statement should be supported by the appropriate data of their National Registry.

Reply 5: In accordance with the reviewer’s suggestion, we added the survival of lung transplantation from the National Registry in Japan as a new Figure 2.

Change in the text: We added the legend of the new Figure 2 as follows(line 355), “Figure 2. Overall survival after cadaveric lung transplantation (CLT) (n = 658), living-donor lobar lung transplantation (LDLLT) (n = 270) and heart-lung transplantation (n = 3) in Japan (A). The 5-year and 10-year overall survival rates were 73.72% and 61.37% after CLT, 73.84% and 62.48% after LDLLT, respectively. The 5-year overall survival was 75.69% after bilateral CLT (308 patients), 71.84% after single CLT (350 patients), 74.53% after bilateral LDLLT (227 patients), and 69.96% after single LDLLT (43 patients) (B). This figure was reproduced from reference (2) with permission from the Japanese Society of Lung and Heart-Lung Transplantation.”

Comment 7: Regarding CLAD, the authors stated that “Compared with CLAD after CLT, CLAD after LDLLT is characterized by development predominantly in the unilateral lung”. Similarly, it is stated “in LDLLT, the immunological features of two different donors may affect the development of CLAD in the unilateral lung”. I do not understand what they mean with “unilateral lung”. Is it that CLAD appears more often in single than in double lung transplants? What does it mean “unilateral lung” in a living donor lobar lung transplant?

Reply 7: Unilateral CLAD means that CLAD occurs only in the right or left lung, i.e. the transplanted lung of the unilateral side, after bilateral LDLLT. CLAD after bilateral LDLLT rarely involves both side of the transplanted lungs. For better understanding, we added a new figure showing unilateral CLAD after LDLLT.

Change in the text: We added the legend of the new Figure 1 as follows (line 351), “Figure 1. Representative image of unilateral chronic lung allograft dysfunction (CLAD) after bilateral living-donor lobar lung transplantation. Lung perfusion scintigraphy demonstrates a perfusion shift to the left unaffected lung in a patient with right unilateral CLAD.”

Comment 8: Why is different CLAD in SCLT vs. LDLLT?

Reply 8: CLAD after bilateral CLT involves both lungs of the transplanted lungs. In contrast, CLAD after single CLT and bilateral LDLLT develops in the right or left transplanted lung. Based on these characteristics of CLAD, we use lung perfusion scintigraphy for early diagnosis of CLAD after single CLT and bilateral LDLLT. The recipients after single CLT have the affected lung with CLAD in one side and the native lung in the other side of the chest, whereas those after bilateral LDLLT have the affected lung with CLAD in one side and the unaffected lung without CLAD in the other side of the chest. This would be a difference in CLAD between single CLT and LDLLT. Because we could not describe the detailed information as above in the limited space of this article, we would appreciate it if you could understand this situation.

Change in the text: No change.

Comment 9: In the authors' experience, the rate of re-transplants for CLAD was higher among SCLT. Were there all cases re-transplants of a previous graft or new de-novo lung transplants of the native contralateral lung? In that case, they should not be considered actual re-transplants.

Reply 9: We performed re-transplantation for 6 patients after single CLT, and 4 patients underwent new de-novo lung transplants of the native contralateral lung, and 2 patients underwent bilateral CLT. Currently, we investigate outcomes of re-transplantation in our hospital in the other research project and will report it in the future.

Change in the text: No change.

Comment 10: Regarding malignancies, the incidence and management of lung cancer after lung transplantation is under reported. May the authors comment more in depth their experience with this subset of patients? Especially considering the high rate of SCLT performed in their series.

Reply 10: We apologize that we didn't have any data on lung cancer after single lung transplantation, and we cannot describe this interesting topic. This will be a research topic of national surgery in Japan in the future.

Change in the text: No change.

Comment 11: Regarding infections and kidney disease, little differences are reported compared to international experience. May the authors emphasize on what they think different with respect to other countries?

Reply 11: The effect of infection on outcomes of lung transplantation is discussed in the other review article of this special issue "Why is the outcome good? Secrets of lung transplantation in Japan." As a result, we reported only the essence of infection management in the long term and did not describe much about infection after lung transplantation. We would appreciate it if you could find the following sentence (line), "The impact of infection on LT in Japan is described elsewhere in this series; here, we will briefly describe the key points regarding infectious complications during long-term care after LT." To tell the truth, we have very little information about chronic kidney disease due to the short history of lung transplantation since 1998 in Japan. The incidence of chronic kidney disease after LT seems to be low in Japan, and we have already emphasized it as in the following sentence (line), "Compared with the ISHLT report, the decreased incidence of dialysis patients after LT might be attributable to the fact that Asian populations have a lower risk of CKD requiring chronic dialysis or KT than Caucasian populations."

Change in the text: No change.

Comment 12. Figure 1B best before 1A. I wish to congratulate the authors for their excellent manuscript.

Reply 12: As the reviewer suggested, we put the former Figure 1B before 1A.

Change in the text: We changed the figure legends of the new Figure 3 (the former Figure 1) (line 362) as follows, "Figure 3. Overall survival after lung transplantation (LT) (n = 213) in our hospital, including cadaveric LT (CLT) (n = 116), living-donor lobar LT (LDLLT) (n = 95), and hybrid LT combining CLT and LDLLT (n = 2) (87). The 5-year and 10-year overall survival rates after LT were 77.1% and 64.9%, respectively (A). Overall survival after LDLLT (n = 95) and bilateral (n = 76) and single CLT (n = 40) in our hospital. No significant differences in overall survival according to LT procedure were seen at our hospital ($P = 0.37$) (B)."