

Peer Review File

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Review Comments

Reviewer A

Abstract:

Comment 1: There are several typographical and grammatical errors throughout the abstract which should be revised.

Reply 1: We are very sorry, but the abstract which we had submitted was un-proofed version. We will submit the English-proofed abstract.

Comment 2: If the goal of this review is to highlight aspects of surgical technique and perioperative care in Japan for lung transplant patients that support good survival despite long waitlist times, in addition to what is already included in the second paragraph, it would be helpful to provide some data on what the waitlist survival. A possibility that is not already discussed, is that it could be just that sicker patients die on the waitlist and outcomes are better because only healthier patients are living long enough to undergo transplant.

Reply 2: We discussed the second point as the following sentences, “Other recipients’ characteristic that may affect the prognosis is the patient’s diagnosis. Because the waiting time is long, patients with a rapidly progressive disease cannot survive until LT”.

Changes in the text: We added the data of the waitlist mortality. We added the following sentence in discussion, “There is a possibility that sicker patients die on the waitlist and outcomes look better because only healthier patients are living long enough to undergo LT.”.

Introduction:

Comment 3: It would be very useful to provide some estimate of waitlist mortality in Japan to as well as median survival and graft survival for lung transplant just to provide more context into whether the good prognosis for lung transplant is due to patient care factors or an artifact of selection bias.

Reply 3: The waitlist mortality is about 37%.

Changes in the text: We added the following sentence; “The waitlist mortality has reached 37% according to data from the Japan Organ Transplant Network.”

Patient Selection:

Comment 4: If the data is available, it would be helpful to show or cite the pulmonary function of candidates at the time of listing, especially since these candidates are having to be listed early.

Reply 4: There was a report from one of the LT centers in Japan. HIRAMA T, AKIBA M, WATANABE T, et al. Waiting time and mortality rate on lung transplant candidates in Japan: a single-center retrospective cohort study. BMC Pulm Med. 2021;21:390.

Changes in the text: We added the following sentence; HIRAMA et al. reported the pulmonary function of LT candidates at the time of listing at Tohoku University Hospital, which is an LT center in Japan (6). According to their report, the predicted forced vital capacity of patients with interstitial lung disease at the time of listing was low, with a median of 44.5% (interquartile range, 30.4%–59.7%).

Comment 5: What is the composition of the selection committees for listing potential lung transplant candidates? Do they just consist of lung transplant surgeons and respirologists?

Reply 5: The second committee consists of five or six respirologists and one or two lung transplant surgeons.

Changes in the text: We added the sentence above in the text.

Comment 6: The formatting of Table 2 makes it very difficult to read.

Reply 6: We modified the table.

Living donor LT:

Comment 7: What percentage of patients receive living donor LT and how do outcomes compare with recipients that receive grafts from cadaveric donors.

Reply 7: Based on the LT number which was described in Table 2, the number of living donor LT was 284 cases out of 1036 all LT cases. The percentage was about 27.4%.

Discussion:

Comment: Interesting discussion and appropriate description of the limitations.

Reply: Thank you very much.

Reviewer B

Comment 1: The Abstract is plenty of grammatical and typographical mistakes. Please re-write.

Reply 1: We are very sorry, but the abstract which we had submitted was un-proofed version. We will submit the English-proofed abstract.

Comment 2: The objective of the review was to address the question of why the prognosis of LT recipients is good in Japan. No data are provided to know which are the Japanese results of LT. Survival curves, 30-day mortality, mortality on waiting list, PGD, complications, management of acute rejection and CLAD, redo-transplants, etc. Comparison of these data with those of the ISLHT registry and other major lung transplant centers should be performed and presented in a revised version.

Reply 2: Mortality on waiting list, one year survival and 5 year survival were summarized in Table 1.

Changes in the text: We added the following sentences in the abstract, “The post-LT 5-year survival for cadaveric LT in Japan was 73.7%, which is better than the figure of 59% in the International Society for Heart and Lung Transplantation Registry reports and 54.3% in the Scientific Registry of Transplant Recipients data from the United States.”.

Comment 3: Average time on waiting list is almost 3 years. Authors should provide mortality rates on waiting list, and potential differences depending on the transplant indication. How many candidates are excluded while on waiting list for clinical worsening?

Reply 3: Candidates are excluded when they become bedridden and they cannot do rehabilitation. There is no data how many alive patients are excluded on waiting list, but we think they are included in the waitlist mortality because they will die soon during the long waiting time.

Change in the text: We added the following sentence, “The waitlist mortality has reached 37.7%”.

Comment 4: It is clear that the age restriction for LT in the transplant population is a major factor that influences the outcomes. What is the rationale for such an age restriction in the Japanese population? Why a 56-years old candidate is not suitable for a bilateral lung transplant?

Reply 4: We think the age restriction is rather “cultural” thing. Japanese government has an age retirement policy. The retirement age was 60 years old when the age restriction of LT was made. The retirement age will become 65 years old in 2025. There is a possibility that LT candidate age restriction goes up when cadaveric donors increase in future.

Comment 5: It is remarkable the high rate of LT indications for hematopoietic stem cell transplantation related pulmonary disease. The authors should comment on the reasons for this observation compared with the non-Japanese population. Also, the higher rate of indications of PAH and LAM should be commented.

Reply 5-1 (about p-HSCT): The largest number of diseases for living donor LT recipients are p-HSCT pulmonary diseases. This reflects that the living donor must be a spouse or a blood relative and there is age restriction to be a living-donor which is usually from 20 to 60 years old. The largest combination of a recipient and living donor(s) is a child and his/her parent/parents. The most common pulmonary disease which needs LT in childhood is p-HSCT pulmonary disease.

Reply 5-2 (about PAH and LAM): Patients with idiopathic PAH and lymphangioleiomyomatosis can usually survive until they receive a new lung or lungs with the help of medication. With the aid of available medication, they can survive until they have chances for LTs.

Changes in the text 5-1: Added the following sentences in the living donor LT, “The largest group of diseases for living donor LT recipients are p-HSCT pulmonary diseases (2). This reflects that the living donor must be a spouse or a blood relative and that there is age restriction to be a living donor, which is usually from 20 to 60 years old. The best combination of a recipient and living donor(s) is a child and his/her parent/parents. The most common pulmonary disease that requires LT in childhood is p-HSCT pulmonary disease. Therefore, patients with p-HSCT are the largest group of living donor LTs.”.

Changes in the text 5-2: Added the following sentence, “With the aid of available medication, they can survive until they have the opportunity for LT.”.

Comment 6: One LT contraindication (table 1) is extensive pleural adhesion, but in Tokyo Lung Transplant Program, 11.9% of transplants underwent some sort of preoperative pleurodesis. Please comment the changing criteria.

Reply 6: The definition of “extensive” pleural adhesion is not precisely written. It is difficult to expect the degree of adhesion in advance of LT. Therefore, we do LT for the patients with pleural adhesion.

Comment 7: Single lung transplantation is the first choice in Japan for non-septic disease. Please provide information regarding survival outcomes comparing single, bilateral and living-donor lung transplants.

Reply 7: 5-years survival were 71.8% for single cadaveric LT, 75.7% for bilateral cadaveric LT and 73.8% for living-donor LT.

Changes in the text: We added the following sentences in the Introduction, “Five-year survival was reported to be 71.8% for unilateral cadaveric LT, 75.7% for bilateral cadaveric LT, and 73.8% for living-donor LT in Japan (2). Table 1 details the waitlist mortality, 1-year survival, and 5-year survival in Japan (2), in the United States (3), and from the International Society for Heart and Lung Transplantation (ISHLT) report (4).”.

Comment 8: Line 161: a simultaneous lung volume reduction of the contralateral native lung is not a novel technique.

Changes in the text: We changed “novel ideas” to “several techniques”.

Comment 9: Lines 176-178: Please clarify why intensivists are not involved in the post-transplant care in some Japanese hospitals.

Reply 9: We think the reason is the small number of intensivists in Japan. The number of intensivists in Japan was 2115 in 2021, which was 16.8 per one million population according to the data from the Japanese Society of Intensive Care Medicine. In the United States, 90.4 intensivists per one million in 2015 according to the American Hospital Association report.

Changes in the text: We added the following sentences, “This is probably because the number of critical care specialists is insufficient in Japan, at only 2115 in 2021 according to the data from the Japanese Society of Intensive Care Medicine (24). This equates to 16.8 critical care doctors per 1 million population, whereas in the United States, there were 90.4 critical care specialists per 1 million in 2015 according to the American Hospital Association report (25).”.

Comment 10: Lines 183-186: Please revise the percentages. It is not correct that only 20% of donors in the US are brain-dead donors.

Reply 10: According to the Scientific Registry of Transplant Recipients data, 2443 LTs were performed in the United States in 2021. The number of donors in 2021 was 13862. Therefore, the utility rate was 17.6%.

Changes in the text: “20%” to “17.6% in 2021”

Comment 11: It seems that bronchoscopy is a major issue in the postop. management of Japanese LT recipients. Please add information regarding immunosuppressive strategies, ventilator management, antimicrobial and antifungal therapy, etc.

Changes in the text: We added the following sentences, “Post-LT medication including immunosuppression, antimicrobial, and antifungal therapies slightly differ among LT

centers, but basic regimens are quite similar. Immunosuppressive therapy consists of calcineurin inhibitor, anti-metabolites, and corticosteroids. Antimicrobial antibiotics are selected on the basis of the sputum cultures of the donor and recipient. Oral itraconazole is administered as a prophylactic antifungal therapy and sulfamethoxazole and trimethoprim mixture as a prophylaxis for pneumocystis infection. Oral valganciclovir is given for 6 to 12 months depending on the sero-status of cytomegalovirus in the Tokyo Lung Transplant Program.”.

Comment 12: The issue of ECMO support is unclearly written. Please provide detailed information regarding the rationale for the initiation of VA-ECMO, VV-ECMO, with hemodynamic and respiratory data supporting this management.

Reply 12: We added the sentences below. If the patient has severe pulmonary hypertension and right heart failure, we select VA-ECMO instead of VV-ECMO.

Changes in the text: Added the following sentences, ECMO can cause multiple complications. Short-term complications include bleeding, thrombosis, hemolysis, renal and neurological injury, concomitant infections, and technical and mechanical problems. Long-term complications reflect the physical, functional, and neurological sequelae of critical illness.

Comment 13: The authors relate the good transplant outcomes on surgical skills and dedication of Japanese surgeons and their involvement in the postoperative care, without the need of ICU teams. They should be congratulated for their ability. However, no concrete data are reported to support this. “The excellent surgical skills lead to a low rate complications of bronchial and vessel anastomoses” but they do not present any of this information.

Reply 1: According to one Review paper, the incidences of airway complications after lung transplantation range from 2% to 33%, even though most transplant centers have reported rates in the range of 7% to 8%. In Tokyo LT program, we only have one airway complication which was bronchus intermedius stenosis out of 109 LT cases (from January 2015 to December 2022). The percentage was 0.9%.

Changes in the text: We added the following sentences, “The incidences of airway complications after lung transplantation range from 2% to 33%, even though most transplant centers have reported rates in the range of 7% to 8% (36). In the Tokyo lung transplant program, we have only experienced one airway complication out of 109 cadaveric LT cases (from January 2015 to December 2022), which was bronchus intermedius stenosis. The percentage was as low as 0.9%, which possibly reflects the

quality of our surgeons' skills.”.

Comment 14: Segmental grafts are presented as a technical option in selected cases. The authors should detail information regarding the reasons for such an extremely rare procedure and their results.

Reply 14: We described it in the living donor LT section.

Changes in the text: We added the following sentences in the living donor LT section, “Nakajima et al. reported six cases of living donor segmental LT in pediatric patients with a median age of 7 years (range, 4–15 years) and a median height of 112.7 cm (range, 95–125.2 cm). (16). They performed six cases of bilateral LT under cardiopulmonary bypass. A basal segment and a lower lobe were implanted in three patients, and a basal segment and an S6 segment were implanted in the other three. There was one hospital death (at 14 days) due to sepsis and one late death (at 9 years) due to leukoencephalopathy. The remaining four patients have been alive for over 9 months. The researchers concluded that living-donor segmental LT was a technically difficult but feasible procedure with acceptable outcomes for small pediatric patients.”.

Comment 15: Conclusions are weak and do not answer the question raised in the objectives.

Reply: modified the conclusions.

Reviewer C

Comment 1: The abstract needs extensive English language editing.

Reply 1: We are very sorry, but the abstract which we had submitted was un-proofed version. We will submit the English-proofed abstract.

Comment 2: line 52 ‘why the prognosis of LT recipients is good in Japan’

I see this statement several times. Please kindly give some figures to support this statement, and preferably also present in conjunction with the ISHLT figures so the readers can easily grasp the differences between International results and Japanese results.

Changes in the text: We added the actual 5-year survival data and new Table to compare the differences.

Comment 3: lines 60-70

Physicians in Japan are forced to 'game' the system, much like the situation in North America before the introduction of the LAS score.

Is there any discussion to replace the 'length of time on waiting list' with some kind of risk scoring system for Japan?

Reply 3: The discussion about the scoring system is ongoing, but we have not reached the conclusion.

Comment 4: Line 123 'ECMO can be initiated with cannulation to femoral vessels' can you elaborate a bit more on the use of intraoperative circulatory support?

Since the majority of cases are done for unilateral LTx, presumably the numbers are small. But for the bilat LTx, how many cases use circulatory support, and how many were ECMO vs CPB? What % of cases were done with?

Reply 4: Almost all bilateral LTs were done under ECMO with central cannulation. Pediatric cases were done with CPB. The case with concomitant cardiac surgical procedures was very rare in Japan. In Tokyo LT program, 2 out of 122 LT cases needed intracardiac repair.

Changes in the text: We added the following sentences, "Bilateral LT are performed under ECMO with central cannulation in most cases. Pediatric cases are often performed under cardiopulmonary bypass. The number of patients who need concomitant cardiac surgical procedures is small."

Comment 5: lines 183-184 'the current rate of using donated cadaveric lungs is >80%' With such a high usage rate of donated lungs, and therefore as the authors stated a high number of marginal lungs, can the authors provide some data on the perioperative complications? Such as PGD III, use of ECMO post LTx, pneumonia, renal failure etc?

Reply 5: We do not have data about PGD III. The number of ECMO use post LTx was small. In Tokyo Lung Transplant program, there was no difference in the ICU days and duration of mechanical ventilation between marginal group and non-marginal group.

Changes in the text: We added the following sentences, "Likely because of this management, we have not experienced an increase in mechanical ventilation duration, ICU stay, or post-op ECMO use in patients receiving transplants from donors with marginal factors in Tokyo."

Comment 6: lines 213-219

For the PAH LTx recipients, is there a policy on the use of post LTx CVVH as a means to maintain strict fluid balance?

See Benazzo et al. J Thorac Cardiovasc Surg. 2022 Feb;163(2):524-535.e3.

Reply 6: There was no policy on the use of post LTx CVVH for the PAH LTx recipients.

Reviewer D

Comment 1: I would strongly recommend a repeat proofreading of the abstract and body of the paper as there are numerous spelling / grammatical errors

Reply 1: We are very sorry, but the abstract which we had submitted was un-proofed version. We will submit the English-proofed abstract.

Comment 2: Line 19-20: It is unclear what the authors are trying to say here.

Reply 2: We corrected sentences.

Comment 3: In several areas throughout the text, the authors mention prognosis of lung transplant recipients as ‘good’ (12-13; 33-34; 51-52) however this term ‘good’ is not defined in the body of the text. While it may be challenging to compare outcomes between countries due to the various differences in patient characteristics and candidacy of donor / recipient, it may be helpful to the readers to define what is considered a good outcome in Japan.

Changes in the text: We added the actual 5-year survival data and new Table to compare the differences.

I commend these authors for their excellent review of this patient population. Thank you again for the opportunity to review this manuscript.

Reviewer E

Comment 1: There are a lot of mistakes of English grammar and spelling in “Abstract”. Please correct them.

Reply 1: We are very sorry, but the abstract which we had submitted was un-proofed version. We will submit the English-proofed abstract.

Comment 2: Please correct the word “pulmonary pneumothorax” (line 46) to “pneumothorax”.

Reply 2: Corrected.

Change in the text: “pulmonary pneumothorax” to “pneumothorax”

Comment 3: The following sentence cannot be understood well “They may have had operations, such as pleurodesis or experienced medical pleurodesis to control the pneumothorax” (line 132).

Changes in the text: We changed the sentence to “Some of them have had surgeries or pleurodesis to control the pneumothorax.”.

Comment 4: The transplant candidates may have to wait for 900 days in Japan. Please describe on the indications for bridge ECMO or bridge mechanical ventilation in Japan. All six patients with a bridge ECMO had an option for living donor lung transplantation?

Reply 4: Three patients were bridged to cadaveric LT, and three patients were bridged to living donor LT in Tokyo as described in the Table. No determined indications for the initiation of bridge ECMO for patients without the choice of living donor LT. We take into consideration how long the patient has already spent since the registration on the waitlist and his/her physical strength. Ability of rehabilitation is very important under the bridge ECMO in order not to lose the physical tolerance for LT, therefore, physical ability is carefully assessed at the time of consideration of bridge ECMO.

Changes in the text: We added the sentences above.

Comment 5: The authors mentioned that the excellent surgical skills lead to a low rate of complications of bronchial and vessel anastomoses. The anastomotic complications were really lower in Japan, compared to other countries? If so, please add some reference.

Reply 5: According to one Review paper, the incidences of airway complications after lung transplantation range from 2% to 33%, even though most transplant centers have reported rates in the range of 7% to 8%. In Tokyo LT program, we only have one airway complication which was bronchus intermedius stenosis out of 109 LT cases (from January 2015 to December 2022). The percentage was 0.9%.

Changes in the text: We added the following sentences, “The incidences of airway complications after lung transplantation range from 2% to 33%, even though most transplant centers have reported rates in the range of 7% to 8% (36). In the Tokyo lung transplant program, we have only experienced one airway complication out of 109 cadaveric LT cases (from January 2015 to December 2022), which was bronchus intermedius stenosis. The percentage was as low as 0.9%, which possibly reflects the quality of our surgeons’ skills.”.

Comment 6: Please correct the word “p-HSCR” to “p-HSCT” (line 297).

Reply: Corrected. Thank you.

Change in the text: “p-HSCR” to “p-HSCT”

Comment 7: Please correct the word “LT: living donor” to “LD: living donor” (line 306).

Reply: Corrected. Thank you.

Change in the text: “LT: living donor” to “LD: living donor”

Reviewer F

Thank you for the opportunity for reviewing this manuscript. In this review, the authors discussed why postoperative outcomes of lung transplantation (LTx) in Japan are favorable by the observation of preoperative status and perioperative management. This paper reviewed the current circumstances of LTx in Japan (5-year survival is reported to be more than 70%). On the other hand, the sustainability of LTx in Japan and how to increase the dedicator of LTx in Japan are considered as the future issues. I have some comments.

Comment 1: The abstract of this manuscript includes a lot of typos. Please check it again. The text also have some typos. Does ‘Contraindications mean contraindications in Table 1? English proofreading is necessary when the revised manuscript will be submitted.

Reply 1: We are very sorry, but the abstract which we had submitted was un-proofed version. We will submit the English-proofed abstract.

Comment 2: Medical consultant is considered as one of the factors for the high usage rate of cadaveric donors in Japan. In the revised manuscript, please make some comments on medical consultant system. In addition, please cite the following manuscript when revising; Hoshikawa Y, et al. Medical consultant system for improving lung transplantation opportunities and outcomes in Japan. *Transplant Proc* 2015;47:746-50.

Reply 2: We described the medical consultant system.

Change in the text: Added the sentences, “One of the reasons of the high lung utilization rate is the “medical consultant system” in Japan, which is a unique partnership between transplant consultant physicians and local physicians that has been developed to maximize the organ utilization rate in Japan since 2002 (28).”

Comment 3: Regarding the outcomes of LTx for pleuroparenchymal fibroelastosis (PPFE), please consider to cite this manuscript: Shiiya H, et al. Outcomes of lung transplantation for idiopathic pleuroparenchymal fibroelastosis. *Surg Today* 2021;51:1276-1284.

Change in the text: We added it to the list of references.

Comment 4: When discussing the risks of postoperative bleeding after LTx for recipients

with pulmonary hypertension, it would be better to cite the following article; Kayawake H, et al. Comparison of living-donor lobar lung transplantation and cadaveric lung transplantation for pulmonary hypertension. Eur J Cardiothorac Surg 2023;63:ezad024.

Reply 4: We do not compare living-donor LT to cadaveric LT. Therefore, we did not add the reference.

Comment 5: The authors stated that LTx requiring some additional procedures has been performed in Japan. When discussing this topic, please mention the hybrid LTx". The authors should cite following articles; Kurosaki T, et al. "Hybrid Lung Transplantation" Combining Living Donor and Cadaveric Lung Transplants: Report of 2 Cases. Transplant Proc 2021;53:2004-2007, Nakajima D, et al. Successful lung transplant cases with ex vivo lung perfusion assessment of extended criteria donor lungs. Gen Thorac Cardiovasc Surg 2022;70:406-412.

Reply 5-1: Thank you. We mentioned the procedure.

Reply 5-2: Ex vivo lung perfusion is not common in Japan. It is still a "clinical research" level. Therefore, we do not cite this report.

Changes in the text: Added the following sentence "Kurosaki et al reported two cases of "Hybrid lung transplantation" combining living donor and cadaveric LTs".

Comment 6: In postoperative management, early tracheostomy has been previously reported to be useful after LTx. Please consider to cite this manuscript; Miyoshi R, et al. Effect of early tracheostomy on clinical outcomes in critically ill lung transplant recipients. Gen Thorac Cardiovasc Surg 2018;66:529-536.

Change in the text: We added the following sentence "Miyoshi et al reported the efficacy of early tracheostomy in LT recipients" and added it the list of references.

Comment 7: Regarding the postoperative prolonged ECMO strategy, the report from Hannover group included a large number of patients. Therefore, please cite this manuscript and add some comments to the discussion. Salman J, et al. Mid-term results of bilateral lung transplant with postoperatively extended intraoperative extracorporeal membrane oxygenation for severe pulmonary hypertension. Eur J Cardiothorac Surg 2017;52:163-170.

Reply 7: Thank you for letting us know.

Change in the text: We added the report to the list of reference.

Reviewer G

The reviewer is honored to review an article about the situation of lung transplantation in Japan. This paper is well written and easy to understand. It is also very interesting in that this paper clearly shows some points about why the outcomes of lung transplantation in Japan is so good. However, there are still several points in typos and grammatical errors in this manuscript. For example, “Ton”, “aA” and “oxygenationECMO” in the second paragraph of the abstract. “who” on line 81 should be “which”. “be vary” on line 177 should be “vary”. So, please check the manuscript again with a professional English editor who is familiar with a scientific writing.

Reply: We are very sorry, but the abstract which we had submitted was un-proofed version. We submit the English-proofed abstract and all sentences were English-proofed again.

Reviewer H

This is a nice review on patient selection, surgical and postoperative management for lung transplantation in Japan.

Comment 1: Please obtain professional English editing.

Reply 1: We are very sorry, but the abstract which we had submitted was un-proofed version. We will submit the English-proofed abstract.

Comment 2: How was the outcome of ECMO bridge and postoperative ECMO?

Reply 2: We lost two recipients out of six bridge ECMO patients at 1 month and 14 months. The number is too small to compare the outcome with non-ECMO bridge patients.

Comment 3: More than half of patients required reoperation for bleeding when ECMO was used. Do you still recommend prophylactic ECMO for IPAH patients?

Reply 3: Good point. Recently, we just started using post-op prolongation ECMO only for patients with severe right heart failure.

Reviewer I

Konoeda and Sato submitted a review article regarding lung transplant management in Japan. They discussed many aspects of the clinical practice in Japan, leading to favorable postoperative outcomes compared to other countries.

The followings are the comments from my side.

Comment 1: If the authors wanted to show the favorable outcomes of lung transplantation in Japan, they should show the data or the reference. Based on them, we

can discuss what is good in the practice in Japan.

Reply 1: Mortality on waiting list, one year survival and 5 year survival were summarized in Table 1.

Changes in the text: We added the following sentences in the abstract, “The post-LT 5-year survival for cadaveric LT in Japan was 73.7%, which is better than the figure of 59% in the International Society for Heart and Lung Transplantation Registry reports and 54.3% in the Scientific Registry of Transplant Recipients data from the United States..”.

Comment 2: This paper should clarify the purpose. If the authors wanted to show the favorable outcomes of lung transplantation in Japan, they should focus on what makes a difference. Otherwise, this review is just an introduction to clinical practice in Japan.

Reply 2: Purpose is in the Introduction, “We review the process of LT candidate selection, transplant surgery itself and perioperative management in Japan to address the question of why the prognosis of LT recipients is good in Japan.”

Comment 3: The authors attributed lung transplants' good survival to Japanese surgeons' quality. On the other hand, the authors described that their surgical techniques are not different from the reported techniques. And almost all surgeons in Japan have LT experience in North America or Europe. Then, why and how are the Japanese surgeons good? It isn't very clear to read. Please describe specific reasons, such as the training system of thoracic surgeons in Japan.

Reply 3: The “basic” surgical techniques of LT in Japan are not different from reported standard techniques. However, many cases in Japan are advanced cases. The good prognosis of living donor LT and low rate of airway complication could show the hood surgeon's quality.

Changes in the text: We added airway complication data.

Comment 4: As the authors stated, a long waiting list raises some difficulties in lung transplant surgery. But, the outcomes in Japan seem good despite those odds. Is this because they only do surgeries for survivors from the long waiting term?

Reply 4: The possibility remains.

Changes in the text: We added the following sentences, “There is a possibility that sicker patients die on the waitlist and outcomes look better because only healthier patients are living long enough to undergo LT.”.

Comment 5: What are the indication criteria for living donor transplantation?

Reply 5: Indication is not different from cadaveric donor transplantation. Only when a patient has suitable living donor(s) who needs to be a spouse or a blood relative and between 20 to 60 years old and the patient and the living donor willingly hope living donor LT, we proceed to the assessment of donor(s).

Comment 6: English editing is required. I found many typos, especially in the abstract.

Reply 6: We are very sorry, but the abstract which we had submitted was un-proofed version. We will submit the English-proofed abstract.

Reviewer J

Have the authors properly reviewed the manuscript? There were so many errors and typos that I would have noticed if I had reviewed it even once that it was painful to peer review. I recommend that the authors themselves review the text properly, rather than having it checked by native speakers or corrected by AI.

Do you expect the reviewers to correct them? I thought it was not that kind of job.

Page 1,

line14: A lLong waiting time

line16: Along with the disease progression of disease

line20: Possible explanations for how we to maintain

line25: TOn the other hand

line28: oxygenationECMO

line282: are also fewer. . An increase

Reply: We are very sorry, but the abstract which we had submitted was un-proofed version. We will submit the English-proofed abstract.

Changes in the text: All typos were corrected

Comment 1: The abstract states that The current prognosis of LT recipients in Japan is good. I am wondering if this expression "good" is an academic one or not. I think good in transplantation is evaluated by survival rate, waiting list mortality, waiting time, etc. I would like you to express that it is good after comparing it with the rest of the world. It would be easier for the reader to understand if there were a figure or table comparing these.

Reply 1: We added the Table 1 to compare the Japanese result to the US and ISHLT.

Changes in the text: We added Table 1 and the following sentences, "Five-year survival was reported to be 71.8% for unilateral cadaveric LT, 75.7% for bilateral cadaveric LT, and 73.8% for living-donor LT in Japan (2). Table 1 details the waitlist mortality, 1-year

survival, and 5-year survival in Japan (2), in the United States (3), and from the International Society for Heart and Lung Transplantation (ISHLT) report (4).”.

Comment 2: The ISHLT guidelines state that age 65 and older is a relative contraindication, but currently there is no age limit and double lung transplants are performed at age 70 and older. is it ethically acceptable to limit it at age 60 or 55? Is the average age of transplant recipients is younger than the world average? I think there should be a table to compare these as well. It is obvious to everyone that age is a major contributor to survival.

Reply 2: We think the age restriction is rather “cultural” thing. Japanese government has an age retirement policy. The retirement age was 60 years old when the age restriction of LT was made. The retirement age will become 65 years old in 2025. There is a possibility that LT candidate age restriction goes up when cadaveric donors increase in future.

Changes in the text 2: We added the following sentences, “According to the Scientific Registry of Transplant Recipients data from the United States, 36.7% of recipients were over 65 years old, while most recipients (46%) were 50 to 64 years old among LT recipients in 2021 (3). This demonstrates that LT recipients in Japan are younger than in other countries, and this age factor is one of the reasons for the good prognosis in Japan.”.

Comment 3: How about comparing the percentage of diseases that receive transplants with the rest of the world? It would be better to have a figure or table for this as well.

Changes in the text: We added the following sentence, “according to the ISHLT registry report (4), the leading cause of LT in the North America between 2010 and 2018 was idiopathic pulmonary fibrosis, followed by chronic obstructive pulmonary disease and cystic fibrosis. In Japan, cystic fibrosis is very rare.”.

Comment 4: PAH does not appear to be a disease that accounts for the majority of lung transplants. Why focus on this disease alone when discussing overall outcomes? Are all cases placed on VA-ECMO after surgery?

Reply 4: Agree.

Changes in the text: We deleted most of sentences about post-op prolongation ECMO and Table and shortened the part.

Comment 5: Also, I don't think the ECMO bridge is unique, so what is the reason for including it in the table?

Reply 5: There is small number of reports about long-term bridge ECMO. We believe

long-term bridge VA ECMO should be specially mentioned.

Comment 6: How much exactly do you do in postoperative management, e.g., frequent bronchoscopy? It is difficult to understand without specifics such as how many times a day it is done and what is done after extubation.

Changes in the text: We added the following sentence, “If the purulent secretion is copious, we perform bronchoscopy twice a day until appropriate antibiotics start working and the secretions decrease.”.

Reviewer K

Abstract:

Comment 1: There are several typos and phrases that need to be reformatted in the abstract. Spelling and grammar would be helpful here.

Reply 1: We are very sorry, but the abstract which we had submitted was un-proofed version. We will submit the English-proofed abstract.

Introduction

Comment 2: Line 38 – when you wrote, “long-term prognosis is unsatisfactory”, we wonder if that is the best way to format it. LT has been considered a life-saving therapy, so we suggest you work on this phrase.

Changes in the text 2: We changed the sentence to “its long-term survival lags behind most other forms of solid-organ transplantation”.

Patient Selection:

Comment 3: Good points were described, especially about the controversy between ISHLT guidelines and the situation in Japan. We suggest you expand a bit in the discussion about age – line 68. It would be best if you trace a parallel to many places where older patients are becoming the most common population on the waiting list, mainly due to IPF. We believe it is important for the reader to compare what is done in Japan and what is done in other places.

Changes in the text 3: We added the following sentences, “According to the Scientific Registry of Transplant Recipients data from the United States, 36.7% recipients were over 65 years old and the majority of recipients which was 46% was 50 to 64 years old among LT recipients in 2021 (3). This shows that LT recipients in Japan tended to be younger than other countries. This age factor is one of reasons for good prognosis in Japan.”.

Comment 4: Excellent discussion about multiorgan Tx and the rationale for single vs. double LTx.

Reply 4: Thank you.

Comment 5: Line 81 – Interesting point about the Japanese Respiratory Society. Please trace a parallel with other sites? USA? Europe?

Reply 5: The Japanese Respiratory Society committee is unique in Japan. In the United States, Canada and England, the lung transplant center selects candidates and put them on the waiting list.

Changes in the text 5: Added the following sentences, The Japanese Respiratory Society committee is characteristic in Japan because in other countries such as the United States (7) and England (8), the LT center itself decides whether the patient is a candidate or not, and then they proceed to put the patient on the waiting list.

Comment 6: Good discussion about LAM and PPFE.

Reply 6: Thank you.

Comment 7: Line 107 – it is a very brief description of LLLT. Can you extrapolate since this modality is especially performed in Japan? Survival, complications, etc.? We believe this can be important for the general reader.

Reply 7: Worked on it.

Comment 8: We believe it is interesting for you to comment on why cystic fibrosis is not discussed in this article. Please give this perspective to the reader.

Changes in the text: We added the following sentence “In Japan, cystic fibrosis is very rare.”.

Comment 9: In the “perioperative management”, line 169, “patients are managed by local respirologists until LT”, this is an interesting point. Again, please work on a comparison to other places where patients are often seen or managed or followed by the LT Team while on the waiting list. It is important for us to understand and compare these dynamics in Japan.

Reply 9: Since the waiting time is long in Japan, the transplant center cannot manage all candidate in terms of manpower or resources. The patients are managed by local respirologist regularly and the LT team sees the candidates once or twice a year.

Change in the text: We added the following sentence “they are seen by the LT team once or twice a year during the waiting time.”.

Comment 10: The references are all consistently well done; the authors only need to check JTD requirements. Most of the time, it is the authors, then the Title of the article....Please check and format accordingly.

Reply 10: Corrected.

Comment 11: Tables are easy to understand and facilitate/illustrate the message that the authors are aiming to give.

Reply 11: Thank you.

This article was a pleasure to read. Very interesting, and sound. Excellent points about the profile of donors in Japan, the rationale for using (or not) ECMO as a bridge, the post-operative management (with or without intensivists in Japan), and the challenges you face in the waiting list management, among others. We hope our comments are helpful for the authors, and some revisions are needed to improve the focus, especially in facilitating the comparison between your scenario and the current status of LTx in centers around the world. The general reader will appreciate that.