

## Peer Review File

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### Review Comments

#### Reviewer A:

Thank you for the opportunity for reviewing this manuscript. This paper reviewed the management of patients awaiting lung transplantation in Japan. The waiting period from listing to lung transplant in Japan is known to be longer than other countries; therefore, managements during the waiting period are very important. This paper is well-written and worth reading. I have only some minor comments.

1) Indeed, vaccination section in the Results stated important points, but most of them were about post-transplant status. This section did not suit the main theme of this manuscript.

Reply 1) Thank you for pointing that out. As the reviewer pointed out, we removed the vaccine part.

Changes in the text:

#### **Vaccination**

~~Lung transplant recipients are immunocompromised owing to immunosuppressive medication to prevent rejection, which is susceptible to respiratory infections. All lung transplant candidates should be reviewed for vaccination status. Appropriate vaccination strategies, including coronavirus disease 2019 vaccination, are recommended to minimize the risk of infection. A recent study showed a weakened antibody response following an mRNA vaccine regimen in recipients compared to controls and substantially lower SARS-CoV-2 IgG titers in recipients compared to controls. Another study showed that the antibody response to the SARS-CoV-2 mRNA vaccine was poor in lung transplant recipients. A few cases of rejection that were likely related to SARS-CoV-2 vaccination have been reported. Tixagevimab/cilgavimab pre-exposure prophylaxis is warranted to reduce breakthrough infection risk in vaccinated lung transplant recipients during omicron waves. Live attenuated vaccines, such as rotavirus, varicella-zoster, measles, mumps, rubella, and intranasal influenza, should be avoided in high-risk patients.~~

2) There were no comments on patients with pulmonary complications after hematopoietic stem cell transplantation. Since the general conditions of these patients often deteriorate rapidly, the managements for these patients are important.

Reply 2) Thank you for your valuable comments. We have added the text.

Changes in the text:

**Pulmonary complications after HSCT**

HSCT is a highly invasive treatment for hematologic malignancies. Late-onset noninfectious pulmonary complications (LONIPCs) are life-threatening complications after HSCT. Five types LONIPCs were reported, including bronchiolitis obliterans (BO), bronchiolitis obliterans with organizing pneumonia, diffuse alveolar damage, lymphocytic interstitial pneumonia, and non-classifiable pneumonia. (12) Pleuroparenchymal fibroelastosis (PPFE) has been reported as an LONIPCs. Some patients with PPFE suffer from recurrent pneumothorax, which is resistant to treatment, leading to poor prognosis. Lung transplantation is not indicated for up to two years after the eradication of a hematological malignancy, and a disease-free interval of five years is ideal. In addition, there must be no severe damage to vital organs such as the liver and kidneys, and no uncontrollable GVHD. If the condition progresses too quickly to wait for a cadaveric lung transplant, living donor lung transplantation is considered according to the standards of each transplantation center. In fact, a report from Japan found that 17 patients received a cadaveric lung transplant while 45 patients received a living donor lung transplant (13).

#### **Reviewer B:**

This manuscript by authors from Chiba University in Japan reports on the findings of a literature study reviewing the management of transplant candidates in Japan while listed for lung transplantation

The public in Japan is faced with a low cadaveric donor rate and thus a high mortality is expected while waiting for transplantation. Waiting times in these severely ill patients may exceed a longer period than hoped for and proper patient management is therefore important

#### Major Comments

##### 1) Listing and de-listing of lung transplant candidates

The authors have summarized all aspects that are of importance to manage while being on the waiting list. However, the debate on when listing or de-listing a patient was not covered.

- Please add a paragraph to discuss selection criteria and timing for listing candidates and criteria for de-listing patients by referring to the literature dealing with these topics. e.g.

Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation.

Leard LE, Holm AM, Valapour M, Glanville AR, Attawar S, Aversa M, Campos SV, Christon LM, Cypel M, Dellgren G, Hartwig MG, Kapnadak SG, Kolaitis NA, Kotloff RM, Patterson CM, Shlobin OA, Smith PJ, Solé A, Solomon M, Weill D, Wijssenbeek MS, Willemsse BWM, Arcasoy SM, Ramos KJ. Heart Lung Transplant. 2021 Nov;40(11):1349-1379. doi: 10.1016/j.healun.2021.07.005. Epub 2021 Jul 24.

Reply 1) Thank you for pointing that out. As the reviewer pointed out, we have added the text.

Changes in the text:

### **Listing and de-listing candidates**

An age limitation is enforced for recipients of lung transplantation in Japan, due to severe donor shortage. At the time of registration to be on the waiting list, the recipient must be under 60 for a single lung transplantation or under 55 for a bilateral lung transplantation. To save as many recipients as possible from one donor, single lung transplantation is a priority in Japan. Unless the candidates have pulmonary artery hypertension (PAH) or chronic respiratory infection, a single lung transplantation is usually first option, and a bilateral lung transplantation is a second option. There is no priority system such as allocation system, based on severity or urgency in Japan. Once candidates are on the list, they must wait their turn. Due to the extremely long waiting time, earlier registration may be necessary in considering disease progression and age, rather than the timing of registration presented internationally (6). Once a recipient is enrolled, we may consider removing them from the waiting list if they no longer meet the eligibility criteria during the waiting time, such as when a vital organ remains irreversibly damaged, a malignancy which is difficult to treat, is diagnosed, rehabilitation is not possible after transplantation, or family members are not available.

2) Inactive system:

Line 120: the authors discuss the possibility of “inactive status” in Japan.

- does this inactive status specifically refer to LAM patients or to all patients? This is not clear.

\* In case this is only effective for LAM patients, then the subheading “Inactive system” should be deleted.

\* In case this applies to all diagnoses, then this paragraph should be discussed later in the manuscript at the end of the paper.

Reply 2) Thank you for pointing that out. As the reviewer comments, we have revised the text and moved it to the end of the paper. Thank you.

Changes in the text:

### **Inactive system**

The Japanese organ-transplant registration system allows recipients to self-determine whether they want to have an “inactive status,” i.e., temporary removal from the waiting list for lung transplantation; when they prefer restoration to an “active status,” they can resume their position on the waiting list where they were originally registered. Common reasons for an inactive status are the stable conditions of recipients with medical care, and the clinical features of LAM patients with a history of inactive status have also been reported (20). Currently the outcome of treatment for PAH has improved, there are many patients of PAH with inactive status. The patients of PAH had higher mortality

risk in first 3 months after lung transplantation than other major diagnoses (19), they need to think about the timing of lung transplantation or optimal drug therapy (44).

#### Minor Comments

3) Grammar/typo's - please correct:

- line 48: "... shortage of donors' lungs ..."; this should be "... donor lungs ...".

Reply 3) Thank you for pointing that out. We have revised the sentence.

Changes in the text:

However, the shortage of donor lungs is one of the most critical issues in lung transplantation, which is a particularly serious problem in Japan.

4) References:

- line 239: reference 11: this reference seems to be incomplete; please add issue and page numbers.

Reply 4) Thank you for pointing that out. We have revised the references.

Changes in the text:

16. Nagata S, Ohsumi A, Handa T, et al. Assessment of listing criteria for lung transplant candidates with interstitial lung disease. *Gen Thorac Cardiovasc Surg* 2023; 71(1):20-26.

#### Reviewer C:

Dr. Suzuki and Prof. Yoshino wrote an interesting review-type paper focusing on the management of patients awaiting lung transplantation in Japan. The viewpoint of this article is unique, but the searching method they used seemed to lack many important papers reported by Japanese lung transplant physicians. Furthermore, some of the references they cited as their evidence seemed old and somewhat irrelevant. In these points, the reviewer tried to make some recommendation to improve the contents of this manuscript, as follows:

1) Line 39-43 should be deleted.

Reply 1) Thank you for pointing that out. As reviewers' comments, we have deleted the sentence.

Changes in the text:

**1. Introduction**

### ~~1.1 Background~~

### ~~1.2 Rationale and knowledge gap~~

### ~~1.3 Objective~~

~~This manuscript is written following xxx checklist (if applicable).~~

2) “1.” (Line 45), “1.1” (Line 46), and “1.2” (Line 57) should be revised.

Reply 2) Thank you for pointing that out. As reviewers’ comments, we have revised the sentence.

Changes in the text:

### ~~1. Introduction~~

### ~~1.1 Background~~

### ~~1.2 Objective~~

3) Ref 2 was published in 2014, which is 8 years ago. Please update a reference supporting the data. It would be advised that the authors should cite a web page of Japanese lung transplant society. (Line 55)

Reply 3) Thank you for pointing that out. As reviewers’ comments, we have revised the text and reference.

Changes in the text:

However, lung transplantation in Japan shows favorable outcomes, with 5-year survival rate was 73.72% for cadaveric lung transplantation and 73.84% for living lung transplantation(2), which is getting better year by year (3-5) and also better than that reported by the International Society for Heart and Lung Transplantation registry.

2. The Japanese Society of lung and heart-lung transplantation in 2022.  
<http://www2.idac.tohoku.ac.jp/dep/surg/shinpai/pg185.html>

4) Searching method should be written more clearly (Line 62-65). Where do the authors cite Table X in their manuscript? The reviewer considers that the authors’ searching method might lack many important papers reported by Japanese lung transplant physicians. The reviewer also thinks that there are not so many papers reported from Japanese lung transplant centers. If this is a review type article, the authors should try to cite as many peer-reviewed papers from Japan as possible.

Reply 4) Thank you for pointing that out. As reviewers’ comments, we have revised the text.

Changes in the text:

A literature search was conducted via PubMed in November 2022 using the following keywords: lung transplantation, waiting, management, recipient, and Japan from 2000 to 2022. 11 papers were retrieved by search. We have also added the peer-reviewed paper from Japan which is related to the management of patients who are waiting on

the list for lung transplantation. Peer-reviewed academic journal articles published in English including International Society for Heart and Lung Transplantation registry report were also included.

5) In the section of assessment of infection (Line 68-76), at least a paper written by Tachibana, et al. (PMID: 29773296) should be cited. Recurrence of DPB was also reported by Chen, et al. (PMID: 16916346)

Reply 6) Thank you for pointing that out. As reviewers' comments, we have revised the text and added references.

Changes in the text:

### **Assessment of infections**

Chronic infections or colonization with resistant organisms are sometimes a problem for lung transplantation and may be contraindications to lung transplantation. This problem is particularly important in patients with bronchiectasis, such as cystic fibrosis, which is uncommon in Japan, or diffuse panbronchiolitis (DPB) (7). *Aspergillus* species(8), nontuberculous mycobacteria(8), and multidrug-resistant bacteria, such as *Burkholderia* species or *Pseudomonas aeruginosa*, are sometimes cultured from these patients (9). These patients tend to have a more rapid decline in respiratory function during the waiting period (10). In addition to sinus surgery and nasal care for chronic rhinosinusitis, long-term macrolide antibiotic therapy has been shown to significantly improve the survival of patients with DPB (11).

7. Chen F, Hasegawa S, Bando T, et al. Recurrence of bilateral diffuse bronchiectasis after bilateral lung transplantation. *Respirology* 2006;11:666-8.

8. Tachibana K, Okada Y, Matsuda Y, et al. Nontuberculous mycobacterial and *Aspergillus* infections among cadaveric lung transplant recipients in Japan. *Respir Investig* 2018;56:243-8.

6) In the section of vaccination, the authors should mention more about general vaccination, such as HBV, mumps, and so on, which is one of the important points in clinical lung transplantation. Although live attenuated vaccines are generally prohibited after lung transplantation, such vaccination is even recommended before lung transplantation. In this article, they focused solely on COVID-19.

7) Reply 6) Thank you for pointing that out. Other reviewer also recommended to remove the vaccine part; we have removed this part.

Changes in the text:

### **Vaccination**

~~Lung transplant recipients are immunocompromised owing to immunosuppressive medication to prevent rejection, which is susceptible to respiratory infections. All lung transplant candidates should be reviewed for vaccination status. Appropriate vaccination strategies, including coronavirus disease 2019 vaccination, are~~

~~recommended to minimize the risk of infection. A recent study showed a weakened antibody response following an mRNA vaccine regimen in recipients compared to controls and substantially lower SARS-CoV-2 IgG titers in recipients compared to controls. Another study showed that the antibody response to the SARS-CoV-2 mRNA vaccine was poor in lung transplant recipients. A few cases of rejection that were likely related to SARS-CoV-2 vaccination have been reported. Tixagevimab/cilgavimab pre-exposure prophylaxis is warranted to reduce breakthrough infection risk in vaccinated lung transplant recipients during omicron waves. Live attenuated vaccines, such as rotavirus, varicella zoster, measles, mumps, rubella, and intranasal influenza, should be avoided in high-risk patients.~~

8) In the section of interstitial lung disease, please cite a paper written by Ikezoe, et al. (PMID: 28800589) and Tanizawa, et al. (PMID: 30165854).

Reply 8) Thank you for pointing that out. As reviewers' comments, we have revised the text and added references.

Changes in the text:

#### **Interstitial lung disease**

ILD is a major indication for lung transplantation in Japan. Approximately one-third of ILD patients underwent cadaveric lung transplantation, whereas approximately 50% died while on the waiting list regardless of their specific diagnosis (15). This outcome is like the mortality rate of all Japanese candidates on the waiting list (16). Idiopathic PPFE and LONIPC with radiological PPFE has better survival on the wait list for Lung transplantation than fibrotic ILD without radiological PPFE (17).

15. Ikezoe K, Handa T, Tanizawa K, et al. Prognostic factors and outcomes in Japanese lung transplant candidates with interstitial lung disease. PLoS One 2017;12:e0183171.

17. Tanizawa K, Handa T, Kubo T, et al. Clinical significance of radiological pleuroparenchymal fibroelastosis pattern in interstitial lung disease patients registered for lung transplantation: a retrospective cohort study. Respir Res 2018;19:162.

9) Regarding the sentence (Line 93), "in the world" should be added.

Reply 9) Thank you for pointing that out. As reviewers' comments, we have revised the text.

Changes in the text:

Interstitial lung disease (ILD) and chronic obstructive pulmonary disease (COPD) are the major registered respiratory diseases for lung transplantation in the world.

10) "50%" should be written as "approximately 50%" (Line 105)?

Reply 10) Thank you for pointing that out. As reviewers' comments, we have revised the text.

Changes in the text:

Approximately one-third of ILD patients underwent cadaveric lung transplantation,

whereas approximately 50% died while on the waiting list regardless of their specific diagnosis (15).

11) “advanced LAM” should be revised. (Line 114)

Reply 10) Thank you for pointing that out our mistake. As reviewers’ comments, we have revised the text.

Changes in the text:

However, it ~~advanced LAM~~ is one of the major indications (approximately 20%) in Japan.

12) Ref 13 was published in 2013. The authors should cite more recent registry report.

Reply 13) Thank you for pointing that out. We totally agree with your comments.

Changes in the text:

Due to its rarity, LAM was a minor indication (0.9%) for lung transplantation in an international survey (19).

19. Khush KK, Cherikh WS, Chambers DC, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report - 2019; focus theme: Donor and recipient size match. J Heart Lung Transplant 2019;38:1056-66.

13) In the section of inactive system, the reviewer might assume that there are so many PH patients.

Reply 13) Thank you for your valuable comment. We have revised text.

Changes in the text:

Currently the outcome of treatment for PAH has improved, there are many patients of PAH with inactive status. The patients of PAH had higher mortality risk in first 3 months after lung transplantation than other major diagnoses (19), they need to think about the timing of lung transplantation or optimal drug therapy (44).

14) In the section of malignancy, “cancer” should be changed into “malignancy”, because cancer means epithelial malignant lesion (Line 151-7). The indication of lung transplantation for Japanese patients with a history of hematologic malignancy was recently reported by Noguchi, et al (PMID:33229173), which should be cited in this article. It might be recommended for the authors to cite two articles about postoperative malignancy in Japanese patients reported by Miyazaki, et al (PMID: 27270709). and Tanaka, et al (PMID:26983711).

Reply 13) Thank you for your valuable comment. We have revised text and added the references.

Changes in the text:



Screening for malignancy is essential when considering the indications for lung transplantation. The risk of malignancy recurrence should be considered in patients with a history of cancer prior to registration. Although malignancy with a high risk of recurrence is a contraindication to transplantation, patients with a low risk of recurrence are candidates for lung transplantation. Pre-transplantation malignancy was associated with the risk of de novo malignancy after lung transplantation (26) but was not associated with an increased risk of mortality at 5 years (27). According to the Japanese national survey, de novo malignancy after lung transplantation was 10.1% and post-transplant lymphoproliferative disorder (PTLD) was the most common malignancy (28). PTLD occurred after both living-donor lobar lung transplantation and cadaveric lung transplantation(29). Among 40 cases undergoing lung transplantation after HSCT, 13 patients who had less than 5 years of disease-free interval experienced no recurrence (30). The waiting time is apparently longer than that in other countries, and periodic screening for malignancy might be important in Japan.

28. Miyazaki T, Oto T, Okumura M, et al. De novo malignancy after lung transplantation in Japan. *Gen Thorac Cardiovasc Surg* 2016;64:543-8.

29. Tanaka S, Chen-Yoshikawa TF, Yamada T, et al. Malignancies after living-donor and cadaveric lung transplantations in Japanese patients. *Surg Today* 2016;46:1415-9.

15) In the section of QOL, the authors provided no references, and therefore they should cite several references as evidence because this is a review type paper. For example, there are several papers analyzing Japanese lung transplant candidates, such as Tokuno, et al (PMID: 32211085 and 32399697) and Ikeda, et al (PMID: 33882928).

Reply 15) Thank you for your valuable comment. We totally agree your comments. We have revised text and added the references.

Changes in the text:

### **Quality of life**

The ultimate goal of lung transplantation is not only to improve survival but also to improve functional outcomes. Improving the HQROL of end-stage lung disease is an important aspect of the physical, psychological, and social limitations due to severe respiratory disease. Poor sleep quality due to anxiety and respiratory symptom was common among candidates who are on the waitlist in Japan (41). Since it is the most appropriate evaluation or questionnaire to assess HQROL, some studies have been reported. Both modified Medical Research Council dyspnea and St. George's Respiratory Questionnaire scores were significantly associated with waitlist mortality (42). The Another study showed that the Mageri Respiratory Failure Questionnaire-26 and the Severe Respiratory Insufficiency Questionnaire were effective and useful measures of HRQOL (43). These parameters can be utilized to improve the allocation system or waiting period mortality in the future.

42. Ikeda M, Oga T, Chen-Yoshikawa TF, et al. Patient-reported dyspnea and health predict waitlist mortality in patients waiting for lung transplantation in Japan. *Respir Res* 2021;22:116.

43. Tokuno J, Chen-Yoshikawa TF, Oga T, et al. Analysis of Optimal Health-Related

Quality of Life Measures in Patients Waitlisted for Lung Transplantation. *Can Respir J* 2020;2020:4912920.

15) There are many deficiencies in the writing of references. In ref 12, no page information is provided., Please check again.

Reply 15) Thank you for pointing that out. We have checked and revised the references.

Changes in the text:

16. Nagata S, Ohsumi A, Handa T, et al. Assessment of listing criteria for lung transplant candidates with interstitial lung disease. *Gen Thorac Cardiovasc Surg* 2023; 71(1):20-26.

#### **Reviewer D:**

I was honoured to have the opportunity to review the manuscript entitled “A review on the management of patients awaiting lung transplantation in Japan”. The authors present a literature review of the japan experience on the management of patients awaiting lung transplantation. For that purpose, they reviewed japan literature from 2000 to 2022. The present manuscript suffers from major weak points that make it completely unsuitable for publication. The authors did not present a single numerical value regarding what they are presenting. The results of their investigation are not presented. They present a general overview of general points to be taken into account when managing patients on waiting list, but without following the minimum standards to be considered a scientific publication. It is surprising that the time-frame of literature search was 2000-2020 but most of references are out of this period or even non-japan experience.

Reply) Thank you for your valuable comments. We totally agree with your opinion, and we have updated some of the literature. For example, Ref 2, 6, 19 are replated to new one. We have revised the methods and main document including ISHLT registry or comprehensive care statement from CHEST to compare with Japan. Total reference number increased from 31 to 44. We believe now our manuscript is getting better. Thank you again.

#### **Reviewer E:**

The authors reviewed on the management of patients awaiting lung transplantation on the waiting list in Japan. I have some comments and suggestion.

1. The description is a bit too abstract, and not practical. As for the details of management in each section necessarily do not have to depend on Japanese reports. I think the authors should include details of pretransplant management in the other

countries and areas.

For example, the authors should comment of the details of live attenuated vaccines which the patients on the waiting list should receive before transplant such as hepatitis B.

Reply) Thank you for your valuable comments. We totally agree with your opinion. As reviewers' comments, we have revised the methods and main document including ISHLT registry or comprehensive care statement from CHEST to compare with Japan. Total reference number increased from 31 to 44. We believe now our manuscript is getting better. We are sorry but other reviewer recommended to remove vaccines section since it is not main topic for this paper, we have removed that part. Thank you for your understanding.

6. Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2021;40:1349-79.

14. Adegunsoye A, Strek ME, Garrity E, et al. Comprehensive Care of the Lung Transplant Patient. *Chest* 2017;152:150-64.

### **Vaccination**

~~Lung transplant recipients are immunocompromised owing to immunosuppressive medication to prevent rejection, which is susceptible to respiratory infections. All lung transplant candidates should be reviewed for vaccination status. Appropriate vaccination strategies, including coronavirus disease 2019 vaccination, are recommended to minimize the risk of infection. A recent study showed a weakened antibody response following an mRNA vaccine regimen in recipients compared to controls and substantially lower SARS-CoV-2 IgG titers in recipients compared to controls. Another study showed that the antibody response to the SARS-CoV-2 mRNA vaccine was poor in lung transplant recipients. A few cases of rejection that were likely related to SARS-CoV-2 vaccination have been reported. Tixagevimab/cilgavimab pre-exposure prophylaxis is warranted to reduce breakthrough infection risk in vaccinated lung transplant recipients during omicron waves. Live attenuated vaccines, such as rotavirus, varicella zoster, measles, mumps, rubella, and intranasal influenza, should be avoided in high-risk patients.~~