Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-22-1716

Review Comments

Reviewer A:

This paper describes the current situation regarding the collaboration of thoracic surgeons and pulmonologists in the treatment and management of lung transplantation and lung transplanted patients. On the one hand, the work provides insight into the current management. It shows the role of pulmonologists according to their workplace in relation to now transplanted patients. The authors point out that further expansion of transplantation cannot continue without the involvement or training of pulmonologists.

The work is coherent and easy to read. Only with regard to the nomenclature would I prefer the pulmonologist. The work is a review tailored for Japan. For an international readership, the reference or comparison with other countries would be interesting.

Reply

I would like to thank reviewer A very much for their comments on the manuscript. With respect to the nomenclature, the terms "respirologist" and "pulmonologist" are both common, but "respirologist" is the one more commonly used in Japan. A clear explanation has now been added as shown below, and it is believed this will bring the manuscript up to international standards (see page 5, line 101 and page3, line 39):

> Pulmonologists (hereinafter referred to as "respirologists", this term being more commonly used in Japan) .

Reviewer B:

Overall: This is a review article which explores the growing need for respirologists in the management of lung transplant patients in Japan. This was very well written and informative. Although the article is specific to Japan, there are likely salient lessons from the Japanese experience for other countries with burgeoning lung transplant programs. The authors do a great job of outlining the current status of lung transplant in Japan and current role of respirologists in the lung transplant process there while providing insight into how the role of respirologists might be expanded to support the growing demand for lung transplant. For non-Japanese, it could be helpful to provide greater context by briefly discuss some of the following:

• How has cooperation with relevant medical sub-specialties worked in other types of organ transplant (e.g. hepatologists and liver transplant surgeons) and has that led to greater ability to transplant those candidates?

Reply

I appreciate the careful review and appropriate comments from reviewer B. Such information will make the manuscript more interesting to readers. Accordingly, the roles of physicians in other types of transplantation in Japan have now been described as shown below (see page 8, line 163):

> Similar trends are also seen in other types of organ transplantation, such as kidney, liver and heart, where transplant surgeons play pivotal roles in the peri-operative management of recipients. However, cooperation with physicians in other types of organ transplantation is better organized than it is in LTx in Japan. For instance, in heart transplantation, cardiologists take on the main care of recipients following surgery, while in kidney transplantation, both nephrologists and urologists support each other to successfully take care of recipients. Also, while not all hepatologists accept the role of being main care providers after liver transplantation, more physicians are involved in such transplantation than in LTx. In this respect, the leadership role of respirologists following lung transplantation still lags behind that in other type of organ transplantation in Japan.

• Similarly, are there lessons that can be taken from the training of transplant physicians in other contexts that can be applied to the training of transplant respirologists?

Reply

This is an important point. Unfortunately, training to become a transplant respirologist requires the acquisition of expertise and professional knowledge of too high a level to be included in the training of respirologists in general in Japan. Nevertheless, the future prospects have now been noted as shown below (see page 11, line 277):

> The management of transplant recipients will, in future, be included in a respirology fellowship program.

• What do you think are major hurdles to expanding lung transplant in Japan that would be improved by better training of respirologists? Expanding the number of patients being listed for transplant? Expanding the number of candidates that can be transplanted by offloading some of the burden of patient management from transplant surgeons? Improving long term outcomes? I think this is alluded to in what is currently written, but could be outlined more explicitly.

Reply

A major hurdle is the erroneous belief that transplant recipients should be managed by thoracic surgeons, which has deprived respirologists of opportunities to be involved in transplant practice. This challenging issue has now been described as shown below (see page 11, line 254):

> Increasing the number of respirologists taking care of LTx recipients is certain to change the circumstances with respect to transplantation in Japan. The more trained respirologists participate in transplantation, the more widely transplantation will be provided to patients, resulting in the growth of candidates and recipients. This change will help transplant practice become widely accepted by the Japanese public and, consequently, will lead to the public acceptance of brain death as well as an increase in the number of donors.

Reviewer C:

This was a well written manuscript entitled Roles of Respirologists in Lung Transplantation in Japan.

General Comments

The authors have taken on a worthwhile endeavor of describing the state of lung transplantation in Japan. This information is useful for the transplant community worldwide.

Specific Comments:
1. Can the authors comment on the number of individuals currently awaiting lung transplant in Japan?

Reply

The number of individuals currently awaiting lung transplants in Japan has now been stated as shown below (see page 5, line 91):

> At the end of 2022, there were 545 candidates on the waitlist of the Japan Organ Transplant Network.

2. Under Respirologists working at lung transplant centers in Japan, from lines 89-92, are the number of deceased donor and living donor transplants per institution total for the transplant programs history as of 2021? If so, can the authors also add the average number of transplants per year per program?

Reply

The text is somewhat confusing. The total number of deceased-donor and living-donor transplants is shown in Figure 3. In addition, the total number of transplant candidates and recipients have been updated from the end of 2021 to 2022. To avoid the confusion, the sentences have been corrected as shown below (see page 8, line 148):

> As of the end of 2022, Kyoto University was the leading center for deceased-donor LTx in Japan (total number 196), followed by Tohoku (n=144) and Okayama (n=120), while living-donor transplantation was mostly carried out in Kyoto (total number 119), followed by Okayama (n=95) and Tokyo (n=26).

3. For the 10 lung transplant centers mentioned, can the authors describe the number of thoracic surgeons and respirologists at each program involved in lung transplant. Are all the programs directed by a thoracic surgeon?
4. As a comparison, can the authors comment on the total number of thoracic surgeons and respirologists in Japan?

Reply

I will answer the two questions together. The number of thoracic surgeons in each program involved in lung transplantation has now been stated as shown below (see page 8, line 146):

> As of 2022, there are 1,538 board-certified general thoracic surgeons in Japan, approximately eight staff surgeons being involved in LTx at each center and roughly 80 thoracic surgeons being engaged in transplantation.
>
> In comparison, as of 2022, there are 7,113 board-certified respirologists in Japan. Most respirologists working at transplant centers provide help and support in transplantation consultations but are not main care providers. It is difficult to define which respirologists are involved at each center and which are not. To avoid confusion and misunderstanding, the number of the physicians is not indicated.

With respect to the lead management of lung transplant recipients, most of the transplant process from candidacy evaluation to peri- and post-operative management is still handled mainly by thoracic surgeons. Although this situation has been changing as already noted, Japan still has a way to go to reach the global standard where LTx represents regular clinical practice for patients with advanced respiratory disease.

5. Regarding roles of respirologist, lung transplant patients in the US are often undergo surveillance bronchoscopy and transbronchial biopsies. Are these procedures typically used in Japan as well? If so are the performed by thoracic surgeons or respirologists.

Reply

Surveillance bronchoscopy is rarely performed, and when transbronchial biopsies are needed, thoracic surgeons carry them out. Bronchosopic procedures have now been added as shown below (see page 5, line 97):

Because of the rarity of LTx and the need for appropriate experience in the developing stage (2000–2009), the entire transplant process from candidacy evaluation to peri- and post-operative management, including immunosuppressive and anti-microbial therapy, medical consultants and bronchoscopic procedures, was handled by thoracic surgeons alone (Figure 2).

6. Are there dedicated programs to train lung transplant respirologist in Japan? i.e. advanced fellowships?

Reply

There is no society-certified program to train lung transplant respirologists in Japan. Each transplant center has its own program, but details are scarce because of the lack of transplant physicians. This is explained on page xxx, line xxx.

7. Can the authors suggest additional ways to expand the role of respirologist in lung transplant in Japan? And training more respirologists in transplant medicine?

Reply

There is a clear need for respirologists to become involved either at transplant or non-transplant centers in order to expand the transplant service and provide higher quality care to patients with advanced pulmonary disease as well as to LTx recipients in Japan. Our suggestion in this respect is given in the paragraph “Current activities to address the future direction of lung transplantation in Japan” (see page 10, line 241).

- Some high-volume transplant centers have started respirologist training programs that accept visiting physicians from non-transplant centers or low-volume centers in order to give them experience in seeing candidates on the waiting list and LTx recipients.
- In other LTx centers, respirologists and thoracic surgeons collaboratively register patients with advanced pulmonary disease with the Japan Organ Transplant Network and also follow LTx recipients in respirology clinics.
- Some LTx centers routinely hold online LTx workshops for pulmonologists, where optimal timing for a referral or basic management of LTx recipients is shared with transplant physicians.
- The future prospects are that management of LTx recipients will be taken up into one of the pulmonology fellowship programs.

Figures:

1. Figure 1 is difficult to read. If possible, I suggest making the figure as well as the legend larger for submission.
2. Also, I recommend avoid using red, blue, and green in the same figure due to readers with color blindness.

Reply

I appreciate Reviewer C's suggestions and have answered their two questions together.

As Reviewer C pointed out, Figure 1 was too complicated to read. Accordingly, Figures 1A and 1B have been made larger, and Figure 1C has been additionally created as new Figure 2. Previous Figure 2 has been renamed as Figure 3. These changes will aid readers' understanding. In addition, the color scheme of Figure 1 has been changed to white, gray and black, as shown below:

Figure 1

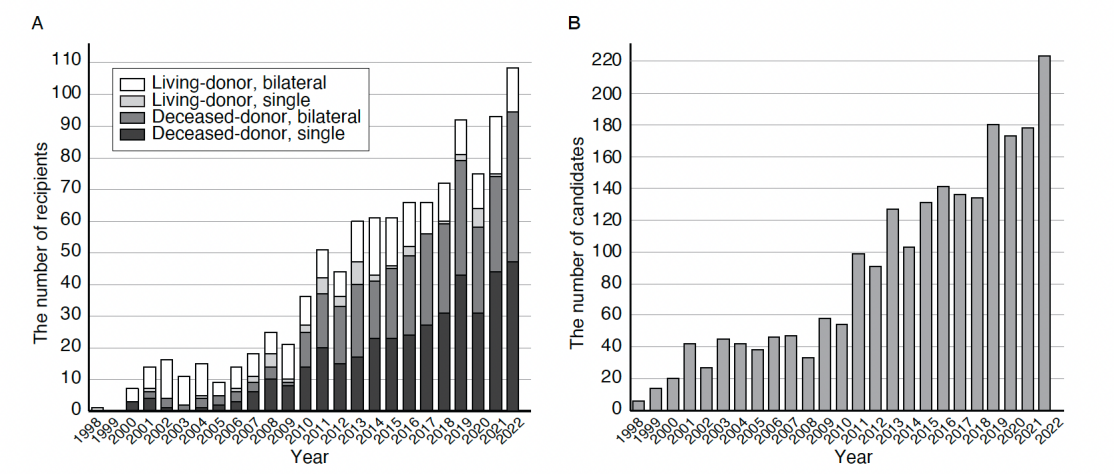


Figure 2

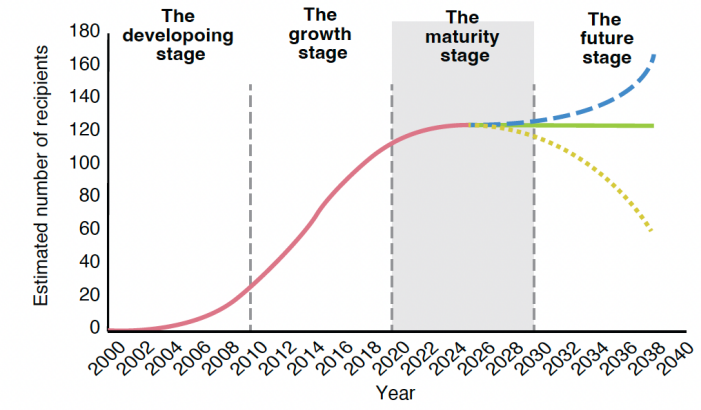
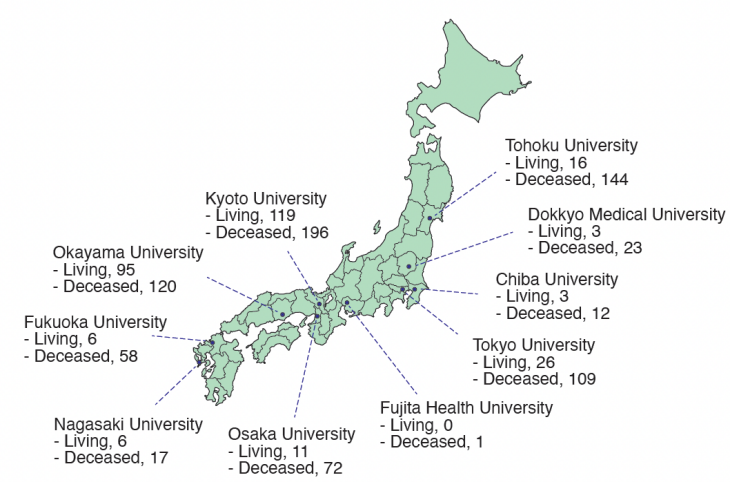


Figure 3



3. For Figure 2, in the description please add time frame for number of transplants

Reply

The time frame has been specified in the captions as shown below:

> Figure 3. Lung transplant centers and volumes in Japan. The total numbers of living- and deceased-donor transplants undergone at each center between 1998 and 2022 are shown.

Reviewer D:

Thank you for the opportunity to review the article titled “Roles of Respirologists in Lung Transplantation in Japan”.
Lung transplantation in Japan is maturing. To increase the number of lung transplantation cases, despite the small number of deceased donors, which is a fundamental issue, the lung transplantation program must be supported by thoracic surgeons as well as multi-disciplinary teams that include respirologists. The roles of respirologists are exceedingly important. In most lung transplantation centers, thoracic surgeons devote themselves to all procedures associated with the procedure, from evaluation of lung transplant candidates to the management of postoperative care. To further improve the lung transplantation system in Japan, respirologists who do not work in transplant centers should be made aware of the best timing for consultation for patients who must undergo transplantation at lung transplant centers. Respirologists must also learn about the management of postoperative care, including immunosuppression and chronic rejection.
In the future, a training program for transplant physicians is required to improve the circumstances surrounding lung transplantation in Japan.
The authors’ responses are well-written, and I have no questions.

Reply

The authors are grateful for Reviewer D’s comments.

Reviewer E:

Thank you for the opportunity for reviewing this manuscript. This paper reviewed the roles of respirologists in lung transplantation in Japan. The maturity of transplant team is important for

the increase of lung transplants, the stability of surgical outcomes, the development of lung transplant and the recruitment of younger physicians. To achieve this goal, respirologists will play more important roles in lung transplants in the future. This paper is well-written and worth reading. I have only some minor comments.

1) The number of references seems small. There were no comments on the system of medical consultant in Japan. This system probably contributes to the higher utilization of donor lungs in Japan. Perhaps, respirologists will play important roles in this system, and they will contribute to the better lung transplant outcomes. Therefore, please make some comments on this system from the standpoint of respirologist.

Reply

This is an important issue from the standpoint of increasing the number of donors in Japan. Although the medical consultation system is described in the topic "Donor management and extremely high donor-utility ratio in Japan" by Yasushi Hoshikawa in the same series, we have now also included a description of the medical consultation system as shown below (see page 5, line 98):

> A medical consultation system for maintaining a donor's lungs in a condition suitable for transplantation is managed by thoracic surgeons from LTx centers. (The system is described in the topic "Donor management and extremely high donor-utility ratio in Japan".)

Fifteen references related to this issue have been added. The search strategy for the references was documented in Methods.

2) Are there any concrete plans to increase and educate lung transplant respirologists in Japan?

Reply

There are no concrete plans to train lung transplant respirologists in Japan. Each transplant center has its own program, but details are scarce because of the lack of transplant physicians. This is described in the comment to Reviewer C and also in the paragraph "Current activities to address the future direction of lung transplantation in Japan" as shown below (see page 10, line 241):

Reviewer F:

This was the review article from Tohoku University, one of the leading lung transplant centers in Japan, describing the past, current, and future role of respirologists in the field of lung transplantation in Japan. The paper is well written and the message the author wants to covey is clear. I feel strong will of the author to make care of transplant recipients in Japan better. Below are my comments and recommendations to strength this review article.

・To my understanding, the sentence "the whole transplant process from candidacy evaluation to postoperative management has been handled only by thoracic surgeons" does not correctly describes the situation in Japan. Most of the process might be handled by thoracic surgeons, but the other physicians took part in the process in "the developing period" or "the growth period". For example, the respirologists have been a member of local and national transplant candidacy evaluation committee. The infectious control team at local transplant center might have a role in the care of transplant recipients such as selecting antibiotics and advising isolation precaution.

Reply

I appreciate Reviewer F's careful review. The phrase "The whole transplant process" has been amended to "Most of the transplant process" (see page 5, line 94, and page 3, line 41).

・It will give much more sense to readers from various countries to provide detail and change about how candidate patient is referred to transplant centers, how the candidacy evaluation is conducted, who takes care during waiting period and how patient is followed up after transplantation in Japan (or at Tohoku University).

Reply

The authors have now included an example of transplant physician activity at Tohoku University Hospital as shown below (see page 10, line 221):

> The following, which relates to Tohoku University Hospital, illustrates how lung transplant physicians play a decisive role in the management of LTx candidates and recipients. Patients with advanced pulmonary disease are referred to Tohoku University Hospital for an extensive evaluation concerning transplant candidacy. The transplant physician explains the risks (such as complications of the transplant surgery, life-long immunosuppression and increased risk of infection) and benefits (greater quality of life, improved functionality and longer survival) of LTx, and informed consent is obtained from the candidates. Close communication between primary care respirologists at a non-transplant center and the transplant physician is essential to transplant success given the long waiting time of over 900 days with an approximately 50% waitlist mortality in Japan. As most candidates deteriorate in the interim, the transplant physician shares the candidates' conditions or newly-developed complications with the respirologists and considers using marginal donor lungs or changing the transplant procedure from single to bilateral LTx. Post-transplant management at a non-transplant center requires the support of the transplant physician with respect to transplant-associated complications, such as graft rejection or cytomegalovirus infection, or optimization of immunosuppressive therapy based on the adverse events or graft function.

・The details of "the number of brain-dead donors was boosted after implementation of the revised Act in 2010" should be presented.

Reply

Details of the Japanese Organ Transplantation Act with respect to brain death have now been included, as shown below (see page 5, line 76):

> Although the 1997 Japanese Organ Transplantation Act legalized the transplantation of lungs from brain-dead donors, few organ donations took place at that time (Figure 1A). The Act required documented consent from donors and did not allow organ donation from children under the age of 15. Thus, the number of deceased-donor LTx surgeries was very small in the first decade, during which time the dominant procedure was living-donor LTx (3). However, the number of brain-dead donors increased after the revised Act became law in 2010, which allows organ donation from brain-dead individuals, regardless of their age, with family consent unless the patients refused organ donation during their lifetime. Consequently, the frequencies of living- and deceased-donor LTx were completely reversed.

Reviewer G:

The manuscript entitled " “Roles of Respirologists in Lung Transplantation in Japan" by Hirama, et al. described the current circumstances about respirologists working on lung transplantation in Japan. They also showed one of passible future directions of the Japanese Lung transplant community. Although this manuscript gives Japanese readers some recommendation (complaints?), it should include more messages for international readers.

Discussion about demerits (and possible merits) of lung transplant teams without respirologists should be added, hopefully, with taking generalized historical backgrounds into account. What factors have been impeding respirologists’ involvement in lung transplant in Japan, just surgeon’s power?

In my opinion, as number of lung transplantation in Japan increases, respirologists would be involved in lung transplantation by necessity. Because of small numbers of lung transplant, more utilization of lungs from extended-criteria donors for relatively severe recipients in Japan than in other countries has been increasing the risk of post-operative complications and might encourage the surgeon-oriented system, although with better outcomes. Generally, a small team with talented members can be superior to a larger team in quality, not in number.

Reply

I am grateful for Reviewer G’s comment that discussion about the possible demerits of lung transplantation without respirologists should be included. The discussion has now been added as shown below (see page 11, line 260):

> In view of the increasing number of organ donations and transplants in Japan, the management of LTx recipients will get out of control if only thoracic surgeons are involved. Additionally, given respirologists’ high degree of expertise in immunosuppressive therapy, based on the recipients’ graft function, and their ability to provide long-term care of recipients with complicated backgrounds and comorbidities, involvement of respirologists at all centers, as well as authorized transplant physicians at transplant centers, is essential for Japanese transplant sustainability