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**Review Comments**

**Reviewer A:**

I enjoyed the excellent review on living lung transplantation in Japan written by Drs. Nakajima and Date. This is s superve summary of their extensive and unique experience in this field. I only have a couple of minor comments as follows.

**Comment 1:** Patients who suffered from pulmonary GVHD after HSCT were reported to be high-risk candidates for lung transplantation, according to the data collected from six transplant centers in Japan (10). P6Ln100
In contrast to the description, the same group from Kyoto has reported extremely good prognosis of this population if a graft was from the same living donor as the primary HSCT [Chen F et al. Am J Transplant 2011]. Also a consistent outcome was also mentioned in the reference #10. I think this is also an important and interesting aspect of living lung transplantation that should be mentioned in the manuscript.
**Reply 1:** We have added the text as advised.
**Changes in the text:** However, the patients who received the graft from the same living donor as for HSCT could show significantly better prognosis. (page 7, line 113)

**Comment 2:** Regarding "living donor surgery outcome (P8Ln156)," it would be helpful to describe operation time, amount of bleeding, median days of hospitalization, mid-long term functional outcomes such as pulmonary function tests and 6-minutes-walk tests if available, in addition to the complications described in the text.
**Reply 2:** We have added the donor outcomes, including operation time, amount of bleeding, and median days of hospitalization.
**Changes in the text:** Median donor surgical time was 282 minutes and median blood loss was 80 ml during donor surgery. (page 10, line 172) Median length of hospital stay was 16 days. (page 10, line 177)

**Reviewer B:**
This is valuable review focused on Living Donor Lobar Lung Transplantation coming from one of the most experienced centers in this field

**Reviewer C:**
I was honoured to review the manuscript entitled "Roles and practice of living-related lobar lung transplantation". This is an interesting and well-written review article analysing the authors' experience on living donor lobar lung transplantation (LDLLT) compared with brain-dead donor lung transplantation (BDLT). The issue is highly interesting and the authors should be congratulated for their outstanding outcomes in such a challenging subset of lung transplant recipients. Some minor comments for the authors are as follows:

**Comment 1:** They comment that after LDLLT, CLAD is usually present in a unilateral graft. I understand that the recipient received a bilateral lobar transplantation from two living donors and that rejection only appears in one of the grafts. It is unclear the reason why LDLLT only develop CLAD in one of the grafts. Some clarification would be welcomed.
**Reply 1:** We have clarified the reason why CLAD typically occurs in the unilateral lung graft after LDLLT.
**Changes in the text:** We have added the following sentences: In conventional bilateral LDLLT, a recipient obtains right and left lobar grafts donated from different living-donors, and thus CLAD due to rejection typically occurs in the unilateral lung graft after LDLLT. (page 9, line 159).

**Comment 2:** One of the objectives of the review was to analysed factors explaining the good outcomes of lung transplantation in Japan. It seems that some factors not explained were the young population receiving lung transplants (30% were paediatric recipients, and adults were all less than 65 years old). This is significantly different from the recipient population depicted in ISHLT Registry.
**Reply 2:** We have explained some factors in the revised paper.
**Changes in the text:** We have added the following sentences: LDLLT recipients were significantly younger than BDLT recipients (median age: 33 years in LDLLT vs. 47 years in BDLT), which might contribute to the good posttransplant outcomes in Japan. (page 6, line 85)

**Comment 3:** It seems surprising that, despite 30% of pediatric recipients no cases of cystic fibrosis were transplanted in Japan. Remarkably, the population receiving transplants for pulmonary graft-versus-host disease following hematopoietic stem cell transplantation was a high as 44 cases of LDLLT and 18 BDLT. Also, the low proportion of COPD recipients should be commented.
**Reply 3:** We have revised the text as advised.
**Changes in the text:** Although cystic fibrosis was the most indication for LDLLT in USA, cystic fibrosis was rarely observed in Japan. Furthermore, chronic obstructive lung disease was not a common indication for lung transplantation in Japan. (page 7, line 106)

**Comment 4:** Looking at the survival curves, there seems to be no significant differences between LDLLT and BDLT.
**Reply 4:** Yes, there was no significant difference in posttransplant survival between LDLLT and BDLT.

**Comment 5**: Given the liberalization of donation after brain death in Japan, might the authors clarify the indications for LDLLT in the more recent period of analysis.
**Reply 5:** As we have described in the introduction, we have constantly needed approximately 20 LDLLT procedures annually in order to overcome a severe issue of donor organ shortage, although the number of BDLT has increased since the

amendment of the Japanese organ transplant law in 2010. Therefore, indications for LDLLT have not changed much even after the increase in BDLT.

**Comment 6:** Is there some activity of donation after circulatory death in Japan?
**Reply 6:** No, we cannot use DCD donor lungs for transplantation in Japan.

**Comment 7:** May the authors add information regarding the use of ECMO in their transplant population?
**Reply 7:** We have described the use of ECMO before, during, and after LDLLT.
**Changes in the text:** Two patients—a 6 year-old boy and 57 year-old woman had been preoperatively managed under ECMO support for 6 days and 104 days, respectively—required a bridge to LDLLT with the use of veno-venous extracorporeal membrane oxygen (ECMO) (pager 6, line 96)

Therefore, cardiopulmonary support is absolutely required during the LDLLT procedure in order to control the blood flow within the implanted lobar grafts: veno-arterial ECMO is basically utilized in the majority of adult transplant cases, whereas cardiopulmonary bypass is employed for pediatric transplantation and/or the cases that require cardiac repair such as closure of an atrial septal defect at the same time. (page 7, line 119)

ECMO support was applied in 10.9% of the post-LDLLT patients. (page 8, line 145)

Again, congratulations to the authors for their remarkable experience on LDLLT.

**Reviewer D:**
The manuscript written by Nakajima describes the roles and practice of living-donor lobar lung transplantation (LDLLT) in Japan. The results of LDLLT in Kyoto University were astonishing, and the authors sufficiently described the summary of recipient characteristics, short- and long-term outcomes, donor surgery, and newly developed techniques to overcome size mismatch in LDLLT in this review. I have just a few minor comments for this excellent review.

**Comment 1:** In line 60, 120, and Table 1, the authors described the lung graft of LDLLT as a “perfect” lung graft. However, there are some disadvantages in the lung graft of LDLLT, including the small size of the graft and the anatomical variations of pulmonary vessels. I recommend the word of “ideal” instead of “perfect.”
**Reply 1:** We have switched the word of “perfect” to “ideal” as advised.
**Changes in the text:** We have switched the word of “perfect” to “ideal” as advised. (page 5, line 66), (page 8, line 133), and Table 1

**Comment 2:** In line 175, the upper limit of the graft volume was defined as 200% in LDLLT. Are there any experimental data about the upper limit of size mismatch in LDLLT? If the reference could be added about this point, this information would be helpful to accept oversized grafts in LDLLT especially for pediatric recipients.

**Reply 2:** No, we do not have any experimental data. However, we have experienced some segmental transplant cases (reference #7). In this case series study, most implanted grafts <200% of the recipient hemithorax functioned well after transplantation, although the oversized graft > 250% of the recipient hemithorax needed downsizing by additional large wedge resection after implantation. Considering these findings, the reasonable upper limit of the graft volume in bilateral living donor lung transplantation is still considered to be 200% of the recipient hemithoracic volume.
**Changes in the text:** We have added the reference #7 as follows: Our upper threshold of the graft volume is considered to be 200% of the recipient's chest cavity volume (7). (page 11, line 194)

**Comment 3:** In line 202, the authors described the technique of the recipient left lower bronchus left closed. Is the bronchial stump of the left lower bronchus covered with some pedicled tissue, such as the pericardial fat pad or the intercostal muscle?
**Reply 3:** We covered the bronchial stump with the pericardial fat pad in a few cases. However, we have recently not covered the bronchial stump and have experienced no bronchopleural fistula postoperatively.

**Reviewer E:**
I really enjoyed reviewing the paper entitled " Roles and practice of living-related lobar lung transplantation" submitted by Kyoto University Lung Transplant Team. First of all, I would like to show great respect to the continuous challenge with excellent results for living-related lobar lung transplantation by Kyoto Team. I think this manuscript shows one of the perfect pictures of LDLLT at present.

I have some questions and the manuscript would be strengthened by addressing the following issues.

**Comment 1:** In the abstract, the segmental lung transplantation is included in established surgical approach of LDLLT. However, as written in the manuscript, segmental lung transplantation especially using S6 segment requires really advanced skill and strategy. Could you show the details of segmental LDLLT (procedure/number) and its long-term/ mid-term results of segmental LDLLT? I want to know the graft-survival of segmental lung grafts. Should we consider the possible future re-LTx after these segmental LTx?
**Reply 1:** We have already described the details of segmental transplantation, including procedures, number, and posttransplant outcomes, in the previous paper which is listed in the references.
Nakajima D, Tanaka S, Ikeda T, *et al.* Living-donor segmental lung transplantation for pediatric patients. *J Thorac Cardiovasc Surg* 2022;doi:10.1016/J.JTCVS.2022.07.031.

Briefly, Between August 2009 and May 2021, we performed living-donor segmental lung transplantation (LDSLT) in six critically ill pediatric patients including one patient on a ventilator alone and another patient on a ventilator and extracorporeal membrane oxygenation (ECMO). There were four male and two female patients, with

a median age of 7 (range: 4-15) years old and a median height of 112.7 (range: 95 to 125.2) cm. The diagnoses included complications of allogeneic hematopoietic stem cell transplantation (n = 4) and pulmonary fibrosis (n = 2). All patients received bilateral lung transplantation 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 patients. In two patients, the right S6 segmental graft was horizontally rotated 180° and implanted as the left lung. Among the nine segmental grafts implanted, seven functioned well after reperfusion. Two rotated S6 segmental grafts became congestive, with one requiring graft extraction and the other venous repair, which was successful. There was one hospital death (14 days) due to sepsis and one late death (9 years) due to leukoencephalopathy. The remaining four patients are currently alive at 9 months, 10 months, 1.3 years, and 1.9 years.

**Comment 2:** Because LDLLT can be indicated only for seriously ill patients who cannot wait for the allocation of brain-dead donors, indication criteria for LDLLT would be different from that of BDLT. Could you comment about criteria for LDLLT? How do you evaluate that the patients cannot wait for brain-dead donors? Is the criteria for LDLLT changing according to the predicted waiting period for BDLT?
**Reply 2:** Indication criteria for LDLLT is basically same as that for BDLT, only except age as described in the text (page 6, line 79). LDLLT is permitted for candidates with age of <65 years, whereas bilateral BDLT for candidates with age of <55 years and single BDLT for age of <60 years. And the indication criteria for LDLLT have never changed at all. Average waiting period for BDLT is currently 900 days in Japan. Therefore, rapidly deteriorating patients cannot wait for 900 days to undertake BDLLT.
**Changes in the text:** In Kyoto University, recipient candidates for LDLLT should be <65 years of age and should meet the conventional BDLT criteria. (page 6, line 79)

**Comment 3:** Is the re-operation of LDLLT/BDLT for recipients after LDLLT more difficult than that after BDLT or similar?
**Reply 3:** Retransplant is similarly difficult. However, after the upper-lobe sparing LDLLT, we can perform the anastomosis of bronchus and vessels at different site from the initial transplant in retransplant procedure, which may make re-operation easier.

**Reviewer F:**
Overall comments to author:
The paper by Daisuke Nakajima et al., entitled ‘Roles and practice of living-related lobar lung transplantation,” is associated with good results of LDLLT in Japan so far and innovations in surgical procedures. Their achievements to date have been outstanding, and the study is potentially of interest to clinicians in the field.
I have the following concerns and comments:

**Comment 1:** Early post-LDLLT outcomes
The incidence of grade 3 PGD within 72 hours after LDLLT and postoperative ECMO support was 12.2% and 10.9%, respectively. The need for ECMO most commonly

arises when severe PGD does not respond to any conventional measures. So, was high PEEP ventilation or another internal medicine unable to control most cases of LDLLT with PGD? The author mentioned that living-lobar grafts are perfect with fewer injuries. Why do you need postoperative ECMO at a rate similar to that after cadaveric lung transplantation in circumstances where donor lungs in good condition can be used ?
**Reply 1:** When we encountered severe PGD, we usually managed patients with high PEEP ventilation, diuretic, position change, and steroid pulse therapy. We used NO in all cases. When these treatments failed to resolve severe PGD, ECMO support was considered to be employed.

The major reason why we required ECMO support was pulmonary edema mainly due to size mismatching between donor and recipient in LDLLT and pulmonary edema due to ischemia-reperfusion injury in BDLT.

**Comment 2:** Long-term outcomes after LDLLT
In LDLLT recipients, are donor-specific antibodies less likely to occur simply because the living donor is a close relative? In the case of bilateral living lobar lung transplants (given that most lung transplants from living donors are bilateral), the HLA of the two living donors differs from that of the recipient. Does this imply that the overall number of mismatches is not significantly different from a cadaveric lung transplant donated by a single donor?
**Reply 2:** Yes, we guess so, but the reason remains unclear, as described in the reference (16). The number of HLA mismatches per donor was significantly lower in LDLLT than BDLT, but we have never compared the HLA mismatches between LDLLT and single BDLT.

**Comment 3:** Lobar graft size match in LDLLT recipient
Concerning donor size, why not combine threshold with either using FVC or 3D-CT volumetory? Please explain the reason for selecting FVC for the lower threshold and 3D-CT volumetory for the upper threshold.
**Reply 3:** We have added the reason as advised.
**Changes in the text:** Functional size matching is important for an undersized lobar graft, whereas anatomical size matching is important for an oversized lobar graft. (page 10, line 183)

**Comment 4:** Strategies for oversize graft
Using this segmental graft has enabled pediatric recipients who would not be eligible for a conventional living lung transplant to undergo transplantation. What are the recipient's minimum age and height requirements to be considered for transplantation?
**Reply 4:** We have recently described the data of the recipients who underwent segmental transplantation in the reference (7). Median age was 7 years old (range: 4-15) and median height was 112.7 cm (range: 95-125.2 cm).

**Comment 5:** Outcomes after novel living-donor lung transplantation
There is a concern regarding the long-term course of living lung transplantation. When

a small graft, especially a segmental graft, is transplanted into a child, the transplanted lung will be stretched as the recipient grows and will eventually need re-transplantation. What percentage of such cases are seen at your institution? Do you believe that LDLLT in children could serve as a bridge therapy before lung transplantation once they reach adulthood?

**Reply 5:** We have experienced a couple of re-transplantation for CLAD after LDLLT, but never experienced re-transplantation for the stretched lung grafts due to pediatric patients' growth. Yes, we agree with the reviewer's opinion that LDLLT could work as a bridge of future BDLT.

**Editorial Comments (Please do not delete this section. Editorial comments should also be replied point by point)**

1: Please provide author contributions in the following format:

(I) Conception and design:
(II) Administrative support:
(III) Provision of study materials or patients:
(IV) Collection and assembly of data:
(V) Data analysis and interpretation:
(VI) Manuscript writing: All authors
(VII) Final approval of manuscript: All authors
Note: With VI and VII, "All authors" is obligatory, while the other credits are case-based.

**Reply1:** We have revised the author contributions as advised.

2. Please kindly confirm if all figures and tables are original and have not been published before. Otherwise, please kindly provide permission.

**Reply 2:** We confirmed that all figures and tables are original.

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**Reply 3:** We have submitted COI disclosure forms.