Low risk donor lungs optimize post-lung transplant outcome for high lung-allocation-score patients

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Abbreviations

cadaveric lung transplant (CDLTx)

lung donor score (DS)

lung allocation score (LAS)

living donor lobar lung transplant (LDLLTx)

lung transplant (LTx)

Organ Procurement and Transplant Network (OPTN)

Abstract

Purpose: The lung allocation score (LAS) has been generally recognized as a contributor to overall survival benefits in lung transplant candidates. However, donor-related risks have never been taken into consideration in previous research that validated the LAS. This study aimed to determine whether the function of LAS as a predictor of posttransplant outcome is influenced by the quality of donor lungs. **Methods:** We retrospectively reviewed 108 patients who underwent lung transplantation (LTx) at Okayama University Hospital since 1998. The cohort was divided into 2 groups by lung donor score (DS; ≤ 4 / > 4). Correlations between LAS and posttransplant outcomes were investigated in both groups. **Results:** In the high DS group, elevated LAS was strongly associated with posttransplant PaO_2/FiO_2 ($p=0.018$). However, in the low DS group, no correlation was found between them. There was no significant difference in long-term survival according to LAS in the low DS group. LAS effectively predicted posttransplant outcome only when lungs with DS > 4 were transplanted. However, LAS was not reliable if high quality lungs were transplanted. **Conclusion:** LTx can be feasible and provides a survival benefit even for a high LAS patient if lungs from a low risk donor are transplanted.

Introduction

Lung transplantation (LTx) has been an established treatment for patients with end-stage pulmonary disease for decades (1). However, accessibility is severely limited by organ availability and waitlist mortality remains high. To maximize the survival benefit of LTx in this situation, a recipient selection policy using lung allocation score (LAS) was implemented in May 2005 by the Organ Procurement and Transplant Network (OPTN) in the United States (2). Currently, the LAS system is regarded as a generally acceptable allocation policy that can reduce waiting time of candidates in serious condition and can improve waitlist mortality in patients with a variety of diagnostic indications for LTx (3). The concept of LAS is based mainly on two factors: waitlist urgency and posttransplant survival probability. The policy of urgency-based prioritization clearly contributes to a reduction in waitlist mortality. Furthermore, some studies that have employed the United States database have concluded that LAS can predict posttransplant outcomes (3-6).

As with the recipient's condition, the donor status has a considerable influence on posttransplant outcome due to serious lung injury following cardiopulmonary resuscitation, lung contusion, airway aspiration, and pulmonary infection at the time of brain insult, as well as the presence of underlying lung disease (7). Therefore, donor factors should be taken into consideration when conducting the validation analysis for the function of the LAS as a predictor

of posttransplant outcome. However, few studies have analyzed the relationship between LAS and posttransplant outcomes by including detailed donor parameters in their studies (8-10). For donor lung assessment, Oto et al first proposed a donor scoring system for LTx that can successfully predict early post-transplant outcomes (11). The lung donor score (DS) includes five standard-donor-criteria factors that are stratified according to severity. This scoring method was validated in previous studies using database of European and North American LTx centers. (12-14)

The United States LAS may be a sophisticated concept that has the potential to provide generalizable insights for different global transplant communities. However, organ utilization rate varies widely in different countries (15-17), and there is also variability in donor lung quality in each LTx case in the different regions. Therefore, a concept that combines recipient and donor factors should be adopted in validation analysis for LAS to draw a universal conclusion. This study was aimed to investigate the function of LAS as a predictor of posttransplant outcomes by donor status, which is represented as the DS.

Material and methods

Patients and recipient selection

This is a retrospective analysis of a consecutive cohort of patients who underwent lung

transplantation at Okayama University Hospital, Okayama, Japan, from October 1998 to August 2015. The cohort consisted of 145 patients who received cadaveric lung transplant (CDLTx) or living donor lobar lung transplant (LDLLTx). Patients who had officially approved indication for LTx were basically registered on the waitlist provided by the Japan Organ Transplant Network (JOTN). LDLLTx was considered for critically ill patients who could not await deceased organ donation. All recipients for LDLLTx met the criteria for deceased LTx, and only healthy blood-relatives within the third degree or a spouse were accepted as living donors by the institutional review board of Okayama University Hospital. Thirty-seven patients with vascular disease were excluded to eliminate bias related to pretransplant medical management and surgical factors. Clinical data recorded until November 2015 were reviewed following approval of our institutional review board (1605-510).

Donor selection and procurement procedure

Available cadaveric lungs were allocated to recipients by the Japan Organ Transplant Network according to waitlist order, ABO compatibility, and matching of predicted pulmonary function value. Detailed donor data including past medical history and results of examination were obtained by authorized donor coordinators. An experienced transplant physician delegated by the transplant network as a consultant for donor management was involved from the early

stage of allocation process. They collected updated donor information about physical, radiological and bronchoscopic findings, and helped local donor hospital staff optimize donor condition as far as possible. The final decision on donor selection was made by our experienced transplant physicians. Lung procurement was standardized for all cadaveric and living donors. The lungs were removed en bloc after antegrade perfusion (60 ml/kg; 4°C, 30 cmH_2O). Donor lungs were routinely flushed with Modified Eurocollins® (Fresenius, Bad Homburg, Germany) (before 2000) or EP-TU solution ® (Cell Science & Technology Institute, Sendai Japan) (since 2000) with prostaglandin added to the flush solution. When the lungs were not damaged, an additional retrograde perfusion through the pulmonary veins was performed on the back table after returning to the recipient's hospital to optimize lung graft preservation. Similarly, in LDLLTx, antegrade and retrograde perfusion with manual ventilation were performed after procurement of the lower lobe.

Lung transplantation procedure and perioperative management

As for indication of the procedure, bilateral or single lung (lobar) transplant was applied for each candidate according to the candidate's primary disease, urgency, and organ availability. Basically, if feasible, single lung transplant and cadaveric transplant were prioritized rather than bilateral transplant and living donation from the point of view of ethicality and effectiveness of

115 organ utilization. Evidence of pathogenic airway organisms or comorbid pulmonary
116 hypertension was regarded as an indication for bilateral rather than single LTx. Regarding
117 technical aspects, an end-to-end anastomosis with a single running suture has most commonly
118 been used. When we performed bilateral LTx, intraoperative cardiopulmonary support with
119 standard bypass technique during the pneumonectomy or the implantation of the lung grafts was
120 mostly used. Recipients received a triple-drug maintenance immunosuppressive regimen
121 consisting of a calcineurin inhibitor (cyclosporine or tacrolimus), cell-cycle inhibitors
122 (azathioprine or mycophenolate mofetil) and steroids. Basiliximab was used as an induction
123 immunosuppressive treatment in recipients with underlying diminished renal function.
124
125 **Stratification of donor lung quality and recipient severity**
126 The quality of each transplanted lung was retrospectively graded by means of a scoring
127 method. The DS was defined according to the previous study by Oto et al (Table 1) (11). Briefly,
128 it includes five variables: age, smoking history, chest X-ray, secretions, and ratio of arterial
129 oxygen tension to inspired oxygen fraction (PaO_2/FiO_2). Each variable received a score between 0
130 and 3, based on clinical importance, with the exception of PaO_2/FiO_2 which was weighted
131 between 0 and 6. The overall DS score ranged from 0 to 18. When there were two donors for
132 bilateral LDLLTx, the higher score was adopted. The LAS of each patient was retrospectively

calculated in November 2015 to determine recipients' pretransplant severity using the LAS calculator on the OPTN website (https://optn.transplant.hrsa.gov/resources/allocation-calculators/las-calculator/). The study population was divided into two groups according to the donor status; the low DS group, DS ≤ 4, and the high DS group, DS > 4. DS > 4 means that at least two variances from the standard donor criteria existed. The two groups were compared regarding background clinical variables (demographics, pulmonary status, surgical variables and donor variables). Correlations between the LAS and posttransplant outcomes (primary graft dysfunction grade, primary PaO_2/FiO_2 ratio, length of ventilator support, tracheostomy requirements, and length of intensive care unit and survival) were analyzed in each DS group.

Statistical analysis

Categorical and continuous variables are summarized as percentage and mean ± standard deviation. Categorical and continuous variables were compared between donor groups using chi-square tests or Mann-Whitney U-tests. Univariate and multivariate regression analysis was performed to determine the influence of various pretransplant clinical variables including LAS on postoperative outcomes. Survival was calculated via the Kaplan-Meier method and compared with the log-rank test. The conventional P value of 0.05 or less was used to determine the level

of statistical significance. All reported P values are two sided. All analyses were performed with SPSS (SPSS 22.0 for windows: SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

One hundred and eight patients were approved as appropriate candidates for lung transplantation by the institutional review board of Okayama University Hospital. The comparative analysis of patient characteristics with regard to DS (high DS vs. low DS) is depicted in Table 2. The mean LAS was 39.1 ± 7.2 in the high DS group and 48.5 ± 15.3 in the low DS group. Patients in the low DS group were significantly younger and had poorer physical activity than patients in the high DS group and a shorter six-minute walk distance (< 150 feet). In addition, time on the waiting list was significantly longer in the high DS group than in the low DS group. The leading indication for LTx was idiopathic pulmonary fibrosis (IPF) followed by chronic obstructive pulmonary disease (COPD) / lymphangioleiomyomatosis (LAM), bronchiectasis (BE), and obliterating bronchiolitis (OB) in the high DS group and IPF followed by OB, COPD / LAM and BE in the low DS group.

Donor and transplant variables

The comparative analysis of donor and transplant variables with regard to DS (high DS vs. low DS) is shown in Table 3. The mean DS was 7.58 ± 2.4 in the high DS group and 1.36 ± 1.3 in the low DS group. The low DS group included a higher proportion of LDLLTx associated with smaller lung volume and shorter organ ischemic time compared with the high DS group. Other variables are comparable in the two DS groups.

Correlation between LAS and posttransplant outcomes by DS group

In the high DS group, elevated LAS was strongly associated with poorer PaO_2/FiO_2 ratio at T72 ($p = 0.018$). In the low DS group, however, there was no association between elevated LAS and posttransplant early graft function. The similar trend was observed in the cohort excluding LDLLTx cases (Figure 1). Univariate analyses examining the correlation between LAS and other early posttransplant outcomes by DS group are shown in Table 4. There was a statistical trend in the high DS group that high LAS was associated with longer duration of ventilator support, ICU stay, oxygen inhalation, and hospital stay after LTx. However, no relation was found in the low DS group. Multivariate regression analysis including LAS and other important clinical variables revealed that LAS was the independent predictor of early graft performance in the high DS group but not in the Low DS group (Table 5).

As for long-term outcome, there was no significant difference in survival between the two

groups (Figure 2, p = 0.820) with a mean follow-up time of 62 ± 55 months (range, 3 to 180 months). During the follow-up, 23 patients died (high DS: n = 5/34, low DS: n = 18/74). Survival after 30 days, 1 year, 5 years, and 10 years was 100%, 89.9%, 77.6%, and 77.6% in the high DS group, respectively, and 98.6%, 91.8%, 77.8%, and 69.6% in the low DS group, respectively. Furthermore, when the recipients in the low DS group were stratified by LAS (LAS < 50 or 50 ≤ LAS), no significant differences in survival between the high and low LAS groups were observed (Figure 3). Survival after 1 year, 5 years, and 10 years were 91.8%, 75.6%, and 64.0%, in the high LAS patients, respectively, and 91.4%, 78.3%, and 73.1%, in the low LAS patients, respectively.

Discussion

This study showed that elevated LAS in the low DS transplantation group was not associated with a worse short-term outcome post-LTx in terms of pulmonary lung function and the length of ventilator support; however, elevated LAS was strongly associated with those parameters in the high DS group. In the survival analysis for the low DS group, the high LAS recipients obtained non-inferiority compared with the low LAS group. Overall, the LAS system effectively predicted posttransplant outcome in patients with non-vascular disease only when extended criteria donor lungs with DS > 4 were transplanted. We utilized the DS proposed by

205 Oto (11) and the LAS by the OPTN as benchmarks to grade the condition of lung donors and
206 recipients. We defined patients with LAS 50 or greater as the high LAS group based on previous
207 reports that have validated the LAS system (4-6). High DS was set at > 4 where a donor had
208 multiple variances from ideal criteria.

209 The study results are supported by other research suggesting that there is a population in
210 which the LAS is not associated with post-LTx outcome. Several studies concluded that patients
211 who needed extracorporeal membrane oxygenation as a bridge to LTx, one of the substantially
212 high LAS groups, showed comparable survival rates to those who did not (18-20). Furthermore,
213 high LAS recipients could survive significantly longer if two lungs were transplanted compared
214 with lower LAS recipients who underwent a single LTx (21). These studies also indicate that the
215 ideal condition for lung donation can secure favorable posttransplant outcomes even for
216 high-LAS recipients. Not only recipient condition but also total graft performance in quality and
217 volume should be considered when predicting outcomes after LTx.

218 We adopted a scoring method to objectively stratify the quality of transplanted lungs. In this
219 study, a negative impact of high DS lungs early after LTx was found as was described in the
220 original research reported by Oto et al (11). While the methodology of scoring donor status has
221 rarely been applied in past papers, this study provides reasonable results compared to other
222 research. Sommer et al reported the importance of selecting stable recipients when marginal lungs

223 are utilized (10). Mulligan et al recently reported that 1-year survival was worse in LTx recipients
224 with LAS 70 or greater when they received extended criteria donor lungs (8). Similarly, the
225 results of the current study based on the scoring method for qualifying donor lungs suggest that
226 optimal lung grafts provided acceptable outcomes even in the high-LAS recipients and that
227 marginal lungs should not be used in marginal recipients. Reasonable results regarding the
228 correlation between donor/recipient risk matching and postransplant outcomes were obtained in
229 this study.

230 Donor lungs transplanted in our series varied greatly in quality and could be ideal study
231 subjects. In Japan, since the rescue allocation system or the LAS has not been established, lung
232 grafts are allocated simply based on the blood type and the order of listing, and 40% of the
233 patients on the waiting list died without receiving a lung transplant (22). Historically, the
234 number of cadaveric organ donations in our country has been extremely low in comparison to
235 other countries (15, 17, 23). Therefore, some peculiar strategies to maximize lung utilization
236 rate have been implemented. First, the nationwide lung donor management policy has been in
237 operation and sends specialized transplant management doctors to the donor hospitals. The
238 system enables lung protection and the acquisition of precise information for donors, leading to
239 a relatively high lung utilization rate (68% per lung) while often using marginal lung grafts
240 (78% per CDLTx) (16, 24). The proportion of extended criteria donor lungs for CDLTx in our

241 institution was 81%, which was much higher than that in previous reports (16, 25). In addition,
242 60% of the marginal lung grafts in our institution had two or more extended criteria in terms of
243 age, smoking history, chest X-ray, secretions or PaO_2/FiO_2. Considering this, the present study
244 includes cases in which severely disqualified lung grafts were transplanted. On the other hand,
245 living donors, who generally offer high quality lungs and are classified in the low DS group, are
246 also included in this study. Such a unique and a wide range of donor characteristics in our study
247 can provide the ideal study platform to verify LAS function and to examine a variety of
248 donor/recipient risk matching models.

249 Patient selection is one of the keys to maintain healthy posttransplant survival outcomes.
250 Extensively high LAS patients are likely regarded as unfeasible lung transplant candidates.
251 However, when focusing on the low DS (< 4) transplant group, we did not find a significant
252 difference both in the early graft function and survival rate over 10 years between the low and
253 high LAS recipients. The data suggest that LAS alone is not an adequate predictor of
254 posttransplant outcome when quality donor lungs are available. However, at the time of each
255 organ offer, our transplant team has defined transplant candidates' feasibility not only by
256 LAS-related factors but also by nutritional state, patient frailty, social support, age matching
257 between donor and recipient, and psychological preparation. Although the LAS by itself could
258 be negligible if low DS lungs were allocated, each decision must be based on other conditions

259 that are not reflected in the LAS mentioned above. Previous studies suggested that recipient
260 characteristics have a greater impact on the results of LTx than graft condition (8, 9).
261 Nevertheless, it is still important that both recipient and donor factors are carefully assessed to
262 identify and optimize the risk of matching between donors and recipients on a case-by-case
263 basis.

264 This study has some limitations. It is a retrospective study on a single-center database of
265 clinical practice over 17 years. We did not account for changes in the lung preservation protocol
266 or recipient management with evolving immunosuppressive regimens over the years. The scale
267 of this study did not allow for statistical analysis to examine the impact of LAS on the basis of
268 recipients' primary diseases. However, we removed patients with pulmonary vascular disease
269 from the research because pretransplant medical management and our operative strategy for
270 patients with pulmonary hypertension had considerably changed over years. Furthermore, we
271 calculated the individual LAS using the website option of the LAS calculator provided by the
272 OPTN website/ UNet^{SM}, under the condition that an LAS system has not been established in our
273 country. Finally, the number of lung transplant recipients included in this study is smaller than
274 studies from other national databases. High LAS–high DS matching case accounted for a small
275 portion in the cohort that potentially affected the results of regression analyses to a certain
276 extent. A nation-wide study with a larger sample size and longer follow-up time is needed for

further validation of the impact of donor score on LAS function as a survival predictor after LTx.

In conclusion, LTx can be feasible and provide survival benefit even for a high LAS patient if lungs from a low risk donor are transplanted. However, high LAS with lungs from high DS donor was associated with a worse primary graft function and a longer ICU and hospital stay. When utilizing low risk donor lungs, the recipient condition, as evaluated by the LAS system, could not properly predict post-LTx outcome.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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Figure legends

Figure 1.

Regression analyses between LAS and post-transplant outcomes. PaO_2/FiO_2 72 hours after transplantation. (DS = lung donor score, LAS = lung allocation score, LTx = lung transplantat, CDLTx = cadaveric lung transplant, LDLLTx = living donor lobar lung transplant.)

Figure 2.

Kaplan-Meier analysis of the survival of lung transplant (LTx) recipients stratified by lung donor score (DS). Number at risk is presented at the bottom of the graph.

Figure 3.

Kaplan-Meier analysis of the survival of lung transplant (LTx) recipients stratified by lung allocation score (LAS) (A) in the high donor score group (High DS) and (B) in the low donor score group (Low DS). Number at risk is presented at the bottom of the graph.