



# Evaluation of the Current Urgency-Based Lung Allocation System in Korea with Simulation of the Eurotransplant Lung Allocation Score

Woo Sik Yu<sup>1\*</sup>, Sun Mi Choi<sup>2\*</sup>, Hye Ju Yeo<sup>3,4</sup>, Dong Kyu Oh<sup>5,6</sup>, Sung Yoon Lim<sup>7</sup>, Young Tae Kim<sup>8</sup>, Kyeongman Jeon<sup>9</sup>, and Jin Gu Lee<sup>10</sup>

<sup>1</sup>Department of Thoracic and Cardiovascular Surgery, Ajou University School of Medicine, Suwon;

<sup>2</sup>Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul;

<sup>3</sup>Division of Pulmonology, Allergy and Critical Care Medicine, Department of Internal Medicine, Pusan National University School of Medicine, Busan;

<sup>4</sup>Transplantation Research Center, Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan;

<sup>5</sup>Department of Pulmonology, Dongkang General Hospital, Ulsan;

<sup>6</sup>Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul;

<sup>7</sup>Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam;

<sup>8</sup>Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul; <sup>9</sup>Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul;

<sup>10</sup>Department of Thoracic and Cardiovascular Surgery, Yonsei University College of Medicine, Seoul, Korea.

**Purpose:** Due to the shortage of lung donors relative to the number of patients waiting for lung transplantation (LTx), more than one-third of patients on the waitlist have died without receiving LTx in Korea. Therefore, the importance of fair and effective allocation policies has been emphasized. This study investigated the characteristics of the current urgency-based allocation system in Korea by simulating the Eurotransplant lung allocation score (ET-LAS) using a nationwide multi-institutional registry for LTx in Korea. **Materials and Methods:** This study used data from the Korean Organ Transplantation Registry (KOTRY), along with additional retrospective data for ET-LAS calculation. A total of 194 patients were included in this study between January 2015 and December 2019. The Korean urgency definition classifies an LTx candidate as having statuses 0–3 according to urgency. The ET-LAS was analyzed according to the Korean urgency status.

**Results:** In total, 92 patients received lung transplants at status 0, 85 at status 1, and 17 at status 2/3. The ET-LAS showed a bimodal distribution with distinct peaks corresponding to status 0 and non-status 0. There was no significant difference in the ET-LAS among non-status 0 patients. In logistic and decision tree analyses, oxygen supplementation methods, particularly oxygen masks and high-flow nasal cannulas, were significantly associated with a high ET-LAS ( $\geq$ 50) among non-status 0 patients.

**Conclusion:** Simulation of the ET-LAS with KOTRY data showed that the Korean urgency definition may not allocate lungs by urgency, especially for patients in non-status 0; therefore, it needs to be revised.

Key Words: Lung transplant, transplant recipients, classification

Received: December 19, 2023 Revised: January 18, 2024 Accepted: March 5, 2024 Published online: May 30, 2024

Co-corresponding authors: Kyeongman Jeon, MD, PhD, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.

E-mail: kjeon@skku.edu and

\*Woo Sik Yu and Sun Mi Choi contributed equally to this work.

•The authors have no potential conflicts of interest to disclose.

© Copyright: Yonsei University College of Medicine 2024

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Jin Gu Lee, MD, PhD, Department of Thoracic and Cardiovascular Surgery, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea. E-mail: csjglee@yuhs.ac

## **INTRODUCTION**

Lung transplantation (LTx) is an established treatment for endstage lung disease.<sup>1</sup> In Korea, the number of LTx procedures has rapidly increased since the outbreak of lung injuries caused by humidifier disinfectants in 2010, increasing from 18 cases in 2010 to 167 cases in 2021.<sup>2-4</sup> Despite this increase in the number of LTx procedures, the number of patients on the LTx waitlist has also increased. As of 2021, 425 patients were awaiting LTx.<sup>2</sup> Due to a shortage of lung donors compared with the number of patients awaiting LTx, 31.8% of patients on the waitlist died without receiving LTx between September 2009 and December 2020.<sup>5</sup> This highlights the importance of having a fair and effective allocation policy.

Korea has an urgency-based lung allocation system that classifies patients into four groups (statuses 0–3), with a lower status indicating a more urgent and higher priority. Status 0 patients are defined as patients admitted to the hospital and dependent on mechanical ventilation (MV) and/or extracorporeal membrane oxygenation (ECMO).<sup>6</sup> Recently, the number of patients who received LTx at status 0 has significantly increased from 49.4% in 2017 to 74.2% in 2021.<sup>2</sup> This rate is significantly higher than the reported rates of 6.4% to 13% in Europe and North America, respectively, which may be associated with poor post-transplant outcomes, especially in patients undergoing  $MV.^{7.10}$ 

To decrease the stagnation of status 0 patients on the waitlist and avoid LTx in excessively debilitated patients from prolonged bridging with MV and/or ECMO, Korean authorities have decided to restrict the duration of stay in status 0 patients who are 19 years or older to a maximum of 3 weeks since May 2023. This may have increased the number of non-status 0 (statuses 1–3) patients who underwent LTx.

The lung allocation score (LAS) was first introduced in the United States in 2005. The LAS was developed to allocate donor lungs based on medical urgency while avoiding futile transplants and replacing wait-based allocation.<sup>11</sup> It ranks patients according to their predicted waitlist and post-transplant survival to determine their transplant benefit. Germany and the Netherlands adopted the LAS for lung allocation, and the LAS was used for the international exchange of donor lungs between Eurotransplant countries.<sup>12</sup>

Previous LAS simulations in a single LTx center in Korea suggested that the Korean urgency statement did not stratify patients by urgency except for status 0.<sup>13</sup> There was no difference in the urgency measure (predicted waitlist survival) and LAS score between non-status 0 patients. However, this finding has not yet been validated in larger cohorts.

The present study aimed to investigate the characteristics of the current urgency-based allocation system in Korea by simulating the Eurotransplant LAS (ET-LAS) using a nationwide multi-institutional registry. We sought to gain insights into the current system and identify potential areas for future improvement.

## **MATERIALS AND METHODS**

#### Patients

The Korean Organ Transplantation Registry (KOTRY) is a prospective multicenter cohort registry that includes lung, kidney, liver, pancreas, and heart transplants in Korea. The KOTRY LTx cohort was initiated in 2015. Patients who underwent LTx between the beginning of the study and December 2019 were enrolled in the present study. Patients who underwent heart-lung transplantation were excluded from this study. As the KOTRY database does not include the detailed preoperative variables required to calculate the ET-LAS, some preoperative variables were gathered retrospectively from each institution. These variables included functional level (assistance required to perform activities of daily living), need for assisted ventilation, requirement of supplemental oxygen, amount of oxygen supplied to maintain adequate oxygen saturation (90%-92%), method of oxygen supplementation, mode of ECMO, and hospitalization. High-flow nasal cannula (HFNC) was defined as an oxygen flow >15 L/min.

# Definition of Korea's urgency-based lung allocation system

Transplant candidates were classified as statuses 0-4 according to urgency. Status 0 corresponded to a hospitalized patient on MV and/or ECMO owing to respiratory failure. Status 1 was defined as the presence of one or more of the following: partial pressure of oxygen (PaO<sub>2</sub>) <55 mm Hg, as measured without oxygen administration; mean pulmonary arterial pressure >65 mm Hg or mean right atrial pressure >15 mm Hg; cardiac index <2 L/min/m<sup>2</sup>; partial pressure of carbon dioxide (PaCO<sub>2</sub>)  $\geq$ 80 mm Hg; or hospitalization for >2 weeks with HFNC (30 L, fraction of inspired oxygen  $\geq 0.6$ ). Status 2 was defined as the presence of one or more of the following: forced expiratory volume in 1 s (FEV<sub>1</sub>) <25%; PaO<sub>2</sub> <60 mm Hg, as measured without supplemental oxygen; average right atrial blood pressure of 10-15 mm Hg; average pulmonary arterial pressure of 55-65 mm Hg; cardiac index <2−2.5 L/min/m<sup>2</sup>; 70 mm Hg≤PaCO<sub>2</sub> <80 mm Hg; or diffusing capacity of the lungs <30% on a pulmonary function test. Status 3 was defined as the presence of one or more of the following: requirement for a single lung transplant; emphysema, pulmonary hypertension, or diffuse interstitial lung disease; <30%; or hospitalization more than three times for respiratory failure.6

#### **ET-LAS simulation**

After the adoption of the LAS system from the US, the Organ Procurement and Transplantation Network (OPTN) LTx committee periodically audited the performance of the LAS system. The LAS has been changed according to the revised calculation. As of March 9, 2023, the LAS has been replaced by the lung Composite Allocation Score.<sup>14</sup> The LAS was adopted in Germany in 2011, in the Netherlands since 2015, and in Italy since 2016.<sup>15</sup> The LAS is also being used in organ exchange within Eurotransplant countries. ET-LAS is based on the US LAS model from 2008 and additionally incorporates the extracorporeal life support (ECLS) factor.<sup>12</sup> The diagnosis of lung disease was categorized into four categories labeled group A (obstructive lung disease), B (pulmonary hypertension), C (cystic fibrosis), and D (restrictive lung disease/interstitial lung disease).<sup>11</sup> The ET-LAS calculation is based on the patient's condition at the time of LTx. The 6-min walk distance (6MWD) of patients in the intensive care unit or those dependent on ECMO was replaced with 0. The calculations were performed using a web-based calculator in November 2021.<sup>16</sup>

#### Statistical analysis

Clinical variables were described as mean±standard deviation and as frequency (percentage) for categorical variables. Continuous variables were compared using one-way analysis of variance (ANOVA). Categorical variables were compared using the chi-squared or Fisher's exact test. Tukey's honest-significant-difference test was performed under the significant results of ANOVA for multiple comparisons. A histogram was drawn, and the bimodality coefficient was calculated to evaluate the distribution of the LAS. A bimodality coefficient >0.555 indicated a bimodal distribution.<sup>17</sup> To propose a new urgency definition for LTx, we conducted binary logistic regression and decision tree analyses to identify factors that predict a high LAS in non-status 0 patients, with the classification based on a cutoff value of 50 for the ET-LAS score, in accordance with Eurotransplant.12 For the binary logistic regression test, variables with a *p*-value $\leq 0.1$  in the univariable analysis were included in the multivariable analysis. The decision tree model was performed with conditional inference trees (CTree) of the party package with all variables tested in the univariate logistic regression

analysis.<sup>18</sup> Survival analysis was performed using the Kaplan-Meier method, and comparisons were made using the logrank test; the *p*-value was adjusted for multiple comparisons.<sup>19</sup> Statistical analyses were performed using R, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). *p*-values <0.05 were considered statistically significant.

#### **Ethics statements**

This study was approved by the Institutional Review Boards of each participating hospital (05-2021-216, 2021-09-064, 4-2021-0987, H-2110-050-1261, and B-1806-474-401). Written informed consent was obtained from all participants before LTx at the relevant institutions for enrollment in KOTRY. However, the requirement for obtaining informed consent for additional data collection from the medical records was waived due to the observational nature of the study.

## RESULTS

#### **Baseline characteristics**

During the study period, 220 patients underwent LTx and were registered in KOTRY. Among them, patients who received heart-lung transplantation (n=4), those from an institution that withdrew their enrollment in KOTRY (n=19), and those who were not available for additional data for ET-LAS calculation (n=4) were excluded. In total, 194 patients were enrolled in this study. Most patients received LTx in status 0 or 1 (92.2%), and 92 patients (47.4%) were dependent on MV and/or ECMO at the time of LTx (status 0) (Fig. 1). Eighty-five patients were classified under status 1, and all were attributed to PaO<sub>2</sub> <55 mm Hg without oxygen administration. There were seven patients classified as status 2, with three due to FEV<sub>1</sub> <25%, and four due to PaO<sub>2</sub> <60 mm Hg without supplemental oxygen. Ten patients were classified under status 3. However, the dataset from KOTRY did not include the specific reasons for their classification.

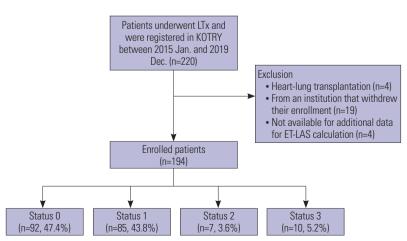


Fig. 1. Flowchart of patient enrollment and distribution of Korean urgency status of study population. LTx, lung transplantation; KOTRY, Korean Organ Transplantation Registry; ET-LAS, Eurotransplant lung allocation score.

#### Table 1. Baseline Characteristics of Patients

	Total (n=194)	Status 0 (n=92)	Status 1 (n=85)	Status 2/3 (n=17)	<i>p</i> value
Age, yr	56.2±9.9	56.2±9.8	55.7±10.5	58.9±7.3	0.464
Male sex	126 (64.9)	65 (70.7)	47 (55.3)	14 (82.4)	0.029
3MI, kg/m²	23.0±3.8	23.1±4.0	22.9±3.8	23.1±3.1	0.935
Diabetes	43 (22.2)	23 (25.0)	14 (16.5)	6 (35.3)	0.155
Primary diagnosis					0.031
IPF	99 (51.0)	42 (45.7)	47 (55.3)	10 (58.8)	
CTD-ILD	32 (16.5)	14 (15.2)	16 (18.8)	2 (11.8)	
Other fibrosis	7 (3.6)	4 (4.3)	3 (3.5)	0 (0.0)	
BOS after HSCT	16 (8.2)	9 (9.8)	6 (7.1)	1 (5.9)	
COPD (emphysema)	9 (4.6)	6 (6.5)	0 (0.0)	3 (17.6)	
Bronchiectasis	8 (4.1)	1 (1.1)	7 (8.2)	0 (0.0)	
IPAH	1 (0.5)	1 (1.1)	0 (0.0)	0 (0.0)	
LAM	8 (4.1)	1 (1.1)	2 (2.4)	0 (0.0)	
ARDS	10 (5.2)	9 (9.8)	1 (1.2)	0 (0.0)	
Re-transplantation	3 (1.5)	2 (2.2)	0 (0.0)	1 (5.9)	
Other	6 (3.1)	3 (3. 3)	3 (3.5)	0 (0.0)	
Diagnosis group	0 (0.17	0 (0. 0)	0 (0.0)	0 (0.0)	0.590
A	19 (9.8)	7 (7.6)	9 (10.6)	3 (17.6)	0.000
В	1 (0.5)	1 (1.1)	0 (0.0)	0 (0.0)	
C	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
D	174 (89.7)	84 (91.3)	76 (89.4)	14 (82.4)	
Hospitalization	171(00.7)	01(01.0)	70 (00.1)	11(02.1)	<0.001
Non-hospitalization	87 (44.8)	0 (0.0)	71 (83.5)	16 (94.1)	0.001
General ward	26 (13.4)	17 (18.5)	9 (10.6)	0 (0.0)	
ICU	81 (41.8)	75 (81.5)	5 (5.9)	1 (5.9)	
Oxygen delivery	01(+1.0)	75 (01.5)	0 (0.0)	1 (0.0)	<0.001
Nasal prong	91 (46.9)	9 (9.8)	67 (78.8)	15 (88.2)	\0.001
$O_2$ flow (L/min)	3.1±1.4	2.6±1.9	3.1±1.3	3.4±1.4	
Mask	11 (5.7)	2 (2.2)	8 (9.4)	1 (5.9)	
$O_2$ flow (L/min)	7.90±3.8	7±7.1	8.5±3.5	5	
HFNC	16 (8.2)	5 (5.4)	10 (11.8)	1 (5.9)	
FiO <sub>2</sub> (%)	53.7±12.1	50±11.5	57.8±11.8	40	
MV		76 (82.6)			
	76 (39.2)		0 (0.0)	0 (0.0)	
FiO <sub>2</sub> (%)	60.5±24.0	60.5±24.0	-	-	-0.001
ECMO	58 (29.9)	58 (63.0)	0 (0.0)	0 (0.0)	< 0.001
FVC (% predicted) <sup>a</sup>	44.1±16.4	45.4±19.6	42.8±13.0	46.8±21.6	0.590
FEV <sub>1</sub> (% predicted) <sup>a</sup>	45.2±19.3	45.6±21.7	46.7±17.5	35.1±18.5	0.154
Mean PAP <sup>b</sup>	26.6±9.9	28.2±9.9	26.9±9.6	15.5±7.9	0.059
6MWD, m <sup>c</sup>	75.0±139.8	0.0±0.0* <sup>†</sup>	145.4±163.4*	180.7±190.6 <sup>†</sup>	< 0.001
Creatinine, mg/dL <sup>d</sup>	0.7±0.6	0.6±0.6*	$0.7\pm0.2^{\dagger}$	1.1±1.2* <sup>†</sup>	0.007
	45.0±12.0	45.6±11.8	44.9±13.0	42.1±7.6	0.579
Wait time, days	139.2±177.6	114.1±196.7*	144.4±133.2	248.7±225.0*	0.014
Donor characteristics	10.0				c
Age, yr	40.0±13.1	41.4±12.6	37.5±13.2	44.6±13.3	0.045
Male sex	119 (61.3)	56 (60.9)	54 (63.5)	9 (52.9)	0.710
Smoker	85 (43.8)	35 (38.0)	44 (51.8)	6 (35.3)	0.140
P/F ratio	463.2±110.0	443.0±103.2*	485.5±96.0*	460.8±178.8	0.036

BMI, body mass index; IPF, idiopathic pulmonary fibrosis; CTD-ILD, connective tissue disease-related interstitial lung disease; BOS, bronchiolitis obliterans syndrome; HSCT, hematopoietic stem cell transplantation; IPAH, idiopathic pulmonary artery hypertension; LAM, lymphangioleiomyomatosis; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; HFNC, high-flow nasal cannula; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; PAP, pulmonary arterial pressure; 6MWD, 6-min walk distance; pCO<sub>2</sub>, partial pressure of carbon dioxide; P/F ratio, partial pressure of oxygen in the arterial blood/fraction of inspired oxygen ratio.

<sup>a</sup>Not available for 62 patients (status 0, n=45; status 1, n=12; status 2/3, n=5); <sup>b</sup>Not available for 132 patients (status 0, n=73; status 1, n=46; status 2/3, n=13); <sup>c</sup>Not available for 11 patients (status 0, n=0; status 1, n=8; status 2/3, n=3); <sup>d</sup>Not available for one patient (status 0, n=0; status 1, n=1; status 2/3, n=0); <sup>e</sup>Not available for 20 patients (status 0, n=0; status 1, n=18; status 2/3, n=2); \*<sup>1</sup>There were significant differences in multiple comparison analysis according to the Tukey honestly significant difference test (*p*<0.05).

Patient and donor characteristics at the time of LTx are summarized in Table 1. The mean age of all patients was  $56.2\pm9.9$ years, and 64.9% of patients were male. Idiopathic pulmonary fibrosis (n=99, 51.0%) was the most common indication for LTx, and there was no significant difference in the diagnosis between the urgency groups. Significant differences were observed in sex, hospitalization, oxygen delivery, ECMO, 6MWD, serum creatinine level, wait time, donor age, and donor PaO<sub>2</sub> in the arterial blood/fraction of inspired oxygen ratio between the urgency groups.

#### **ET-LAS simulation**

The ET-LAS showed bimodal distributions with modes at 37.9 and 89.5 (bimodality coefficient: 0.793) (Fig. 2). Although status 0 patients had a significantly higher ET-LAS score (79.2 $\pm$  19.4) compared to both status 1 (42.8 $\pm$ 10.9) and status 2/3 patients (37.3 $\pm$ 8.6), there was no significant difference between status 1 and status 2/3 patients (Fig. 3A).

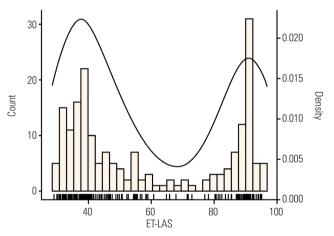


Fig. 2. Histogram of Eurotransplant lung allocation score (ET-LAS).

#### Proposal of a new definition of urgency status

The ET-LAS simulation showed that the current Korean urgency definition may not classify patients by urgency, especially for non-status 0 (statuses 1-3). We conducted logistic regression and decision tree analyses with non-status 0 patients to propose a new definition of urgency status that classified non-status 0 patients into high- and low-LAS categories, with the classification based on an ET-LAS cutoff of 50. In multivariable logistic regression analysis, the use of HFNC was significantly predictive of a high LAS (Table 2). Our decision tree model classified patients into two groups based on their oxygen delivery methods. Patients who required HFNC or an oxygen mask were classified into the high-LAS group, whereas those who required nasal prongs were classified into the low-LAS group (Fig. 4). We compared the ET-LAS scores of the proposed urgency classification using a decision tree model. All groups showed significantly different and stratified ET-LAS (Fig. 3B).

#### One-year survival after LTx

We compared the 1-year post-transplant survival rates between urgency classifications. Under the current urgency classification, patients with status 0 had significantly poorer survival than those with status 1 (Fig. 5A). We classified the non-status 0 patients into two groups according to the ET-LAS: ET-LAS  $\geq$ 50 and ET-LAS <50. The ET-LAS <50 group demonstrated significantly better survival compared to the status 0 group, whereas no significant difference in survival was observed between the ET-LAS  $\geq$ 50 and other groups (Fig. 5B). Furthermore, when we classified the non-status 0 patients according to the proposed urgency classification from the decision model, the nasal-prongs group showed significantly better survival compared to the status 0 group. However, no significant difference in survival was observed between the mask or HFNC group and the other two groups (Fig. 5C).

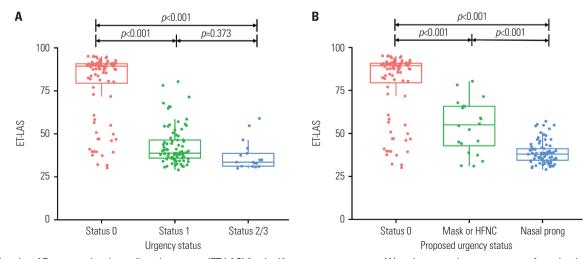


Fig. 3. Boxplot of Eurotransplant lung allocation scores (ET-LAS) for the Korean urgency groups (A) and proposed urgency groups from the decision tree model (B). HFNC, high-flow nasal cannula.

Table 2. Factors Related to a High LAS in Non-Status 0 Patients (ET-LAS ≥50) according to Logistic Regression Analysis	

Variable	n -	Univariable			IV	Multivariable (n=85)		
Variable		OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value	
Age	102	0.998	0.952-1.051	0.921				
Male sex	102	1.190	0.432-3.484	0.741				
BMI	102	1.037	0.904-1.181	0.587				
Diabetes	102	2.275	0.702-6.879	0.152				
Diagnosis group	102							
А		Reference						
D		2.750	0.485-51.895	0.348				
Hospitalization	102							
Non-hospitalization		Reference						
General ward		7.115	1.679-32.295	0.008	1.673	0.207-12.762	0.615	
ICU		1.138	0.057-7.854	0.909	0.293	0.007-4.963	0.447	
Oxygen delivery	102							
Nasal prong		Reference			Reference			
Mask		13.393	2.944-66.613	<0.001	8.674	0.975-119.938	0.067	
HFNC		18.750	4.601-88.577	<0.001	39.854	5.329-529.648	0.001	
FVC (% predicted)	85	0.963	0.928-0.995	0.032	0.797	0.593-0.948	0.081	
FEV1 (% predicted)	85	0.884	0.818-0.940	<0.001	1.072	0.942-1.302	0.444	
Mean PAP	43	0.957	0.866-1.038	0.348				
6MWD	91	0.997	0.992-1.000	0.107				
Creatinine	101	1.607	0.719-5.205	0.248				
pCO <sub>2</sub>	82	1.017	0.974-1.060	0.415				

LAS, lung allocation score; ET-LAS, Eurotransplant lung allocation score; OR, odds ratio; CI, confidence interval; BMI, body mass index; ICU, intensive care unit; HFNC, high-flow nasal cannula; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; PAP, pulmonary arterial pressure; 6MWD, 6-min walk distance; pCO<sub>2</sub>, partial pressure of carbon dioxide; Inf, infinity.

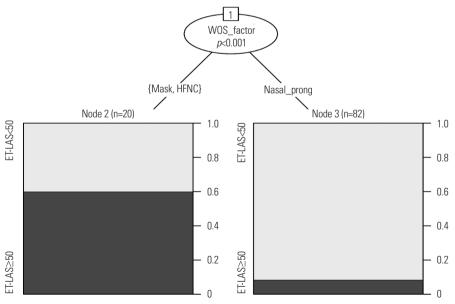


Fig. 4. Decision tree model for predicting high lung allocation score (ET-LAS ≥50). HFNC, high-flow nasal cannula; ET-LAS, Eurotransplant lung allocation score.

## DISCUSSION

The ET-LAS showed a bimodal distribution with modes at 37.9 and 89.5, which corresponded to status 0 and non-status 0, respectively. The ET-LAS between the urgency groups was not

significantly different, especially for non-status 0 (statuses 1–3). The oxygen delivery method was the deciding factor for classifying between a high LAS (ET-LAS  $\geq$ 50) and a low LAS (ET-LAS <50) among non-status 0 patients in the multivariable regression and decision tree analyses. In the survival analysis,

1.00

0.75

0.50

0.25

0.00

Status 1

Status 2/3

С

0

192

85

17

0

1.00

0.75

0.50

0.25

0.00

0

20

82

Number at risk

Survival probability

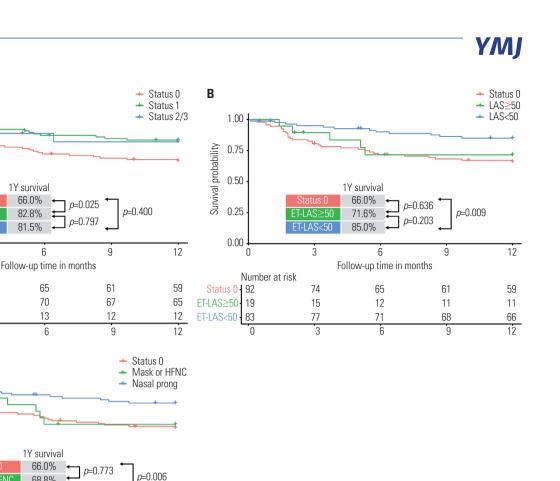
Status 0 Mask or HFNC

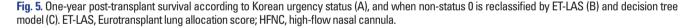
Nasal prong

Number at risk

A

Survival probability





12

59 12

65

12

status 0 patients had a significantly poorer 1-year survival compared to non-status 0 patients with low LAS. However, there was no significant difference in survival between status 0 and non-status 0 patients with a high LAS (Fig. 5B).

1Y survival

66.0%

82.8%

81.5%

6

65

70

13

6

66.0%

68.8%

86.0%

6 Follow-up time in months

65 13

70

6

p=0.087

ġ

61

12 67

9

Status 2

3

74

78

14

3

c or HFNC

3

74 17

75

3

Although the LAS in the US was originally designed to reflect both urgency (waitlist survival) and post-transplant survival, the urgency measure was double-weighted compared to the posttransplant survival measure.11 Therefore, the LAS showed more correlation with urgency than post-transplant survival in a single-center retrospective study.<sup>13</sup> In the current study, status 0 patients had a very high ET-LAS, and there was no significant difference in the ET-LAS among the urgency groups except for status 0. This suggests that the current Korean urgency definition may not effectively stratify patients by urgency, except for those with a status of 0. All status 1 patients were classified based solely on the PaO<sub>2</sub> <55 mm Hg criterion, and other criteria were not utilized. This suggests that patients with less urgency could exhibit hypoxemia (PaO2 <55 mm Hg without oxygen administration) prior to meeting the HFNC requirements, or the criteria for pulmonary hypertension and hypercapnia.

This was in line with our findings of a wide range of ET-LAS scores within status 1.

Under the current system, patients with a higher LAS who are not dependent on MV or ECMO do not receive priority compared with patients with a lower LAS. Priority was given only to patients who were dependent on MV or ECMO. This disparity may be one of the reasons for the bimodal distribution of the LAS and the higher proportion of patients dependent on MV or ECMO in LTx in Korea than in other countries. The recent revision of lung allocation policies in Korea, which now limits the maximum duration of stay for status 0 patients aged 19 years or older to 3 weeks, aims to alleviate the stagnation of status 0 patients and increase the number of LTx recipients in non-status 0 categories. Here, it is more import to classify the non-status 0 patients by urgency.

To explore ways to improve this problem, we conducted multivariable logistic regression and decision tree analyses to identify the factors related to a high LAS in non-status 0 patients. Oxvgen delivery was a significant factor in both analyses. Among non-status 0 patients, those with an oxygen mask or HFNC had a significantly higher LAS compared to those with a nasal prong (Fig. 3B). However, granting priority for lung LTx solely based on the oxygen delivery method has some limitations. First, the LAS range for patients using a mask or HFNC was wide (31–80). Some patients with a low LAS may receive priority for a donor lung. Additionally, when employing these criteria, the preference for oxygen delivery may change to favor the use of an oxygen mask or HFNC, and the expected results may not be realized.

Introducing the LAS instead of the current Korean urgency definition can be a solution for allocating the donor lung by urgency. However, donor lungs are allocated to more urgent patients in the LAS system, which might worsen post-transplant survival. In the current study, the non-status 0 and low-LAS (<50) groups had the best 1-year post-transplant survival (Fig. 5B). However, if the LAS is introduced, more donor lungs will be allocated to non-status 0 and high-LAS ( $\geq$ 50) patients who did not exhibit superior 1-year survival rates when compared with status 0 patients (Fig. 5B).

However, post-transplant survival did not worsen after the introduction of the LAS in the US and Germany. Egan, et al.<sup>20</sup> investigated the effect of the LAS on LTx in the US after its introduction using the OPTN database. They found a 20% increase in the number of LTx procedures and a >40% decrease in wait-list deaths, which were not related to an increase in donors. Despite the increased recipient age and the presence of more patients with lung fibrosis, the 1-year post-transplant survival improved. Germany had an urgent allocation before LAS implementation. Two-thirds of patients with urgent or highly urgent status received LTx, and a higher proportion of patients in Germany were dependent on MV or ECLS before LTx compared with patients in the US.<sup>8</sup> After LAS adoption in Germany, wait-time and waitlist mortality decreased, and the 1-year post-transplant survival improved.<sup>8</sup>

Another concern regarding the acceptance of the LAS in Korea is that it has never been validated among Korean LTx candidates. Additionally, the absence of a comprehensive nationwide database for LTx candidates in Korea poses a substantial challenge in calculating the LAS, which relies on a diverse range of clinical, functional, and laboratory data. The Korean Network for Organ Sharing (KONOS) currently manages the waitlist and allocates organs from deceased donors in Korea. However, it is important to acknowledge that the KONOS currently does not request detailed functional and laboratory results, such as pulmonary function tests (PFTs), 6MWD assessments, and rightsided catheterization data. In the present study, PFT data were unavailable for 32.0% of patients, and right-sided catheterization data were missing for 68.0% of patients.

In the LAS calculation where data are missing or expired, current practices involve substituting such values with normal or least-beneficial values. This approach encourages a thorough evaluation of patients and ensures that data are updated. Therefore, Korean government authorities, such as the KONOS, should promote thorough preoperative evaluations and collect relevant data. By effectively accumulating and using these data, the Korean LTx community and relevant authorities can accomplish two critical objectives. First, validation of the LAS score can be possible for Korean LTx candidates and it can be tailored for the Korean population. Second, the gathered data can serve as a foundation for developing a customized allocation system that aligns with the needs and nuances of the Korean context.

Although this study is the first to provide information on the characteristics of the current urgency-based allocation system in Korea using a multicenter cohort study, several limitations should be acknowledged. The significance of our findings might have been influenced by the inherent selection bias of this being an observational study. Although KOTRY is a prospective registry, we needed to collect data retrospectively to calculate the ET-LAS. Additionally, some patients had missing values, such as PFT and right-sided catheterization data. The missing values were replaced with the least beneficial values in the LAS calculation. Therefore, the LAS could have been underestimated.

In conclusion, simulation of the ET-LAS with KOTRY data showed that the Korean urgency definition may not allocate lungs by urgency, especially for patients in non-status 0. However, more comprehensive data are required to validate this finding, and a customized lung allocation system should be developed for the Korean population based on these data.

### ACKNOWLEDGEMENTS

This research was supported by the "National Institute of Health" research project (2014-ER6301-00, 2014-ER6301-01, 2014-ER6301-02, 2017-ER6301-00, 2017-ER6301-01, 2017-ER6301-02, 2020-ER7201-00, 2020-ER7201-01, 2020-ER7201-02, 2023-ER0805-00).

### **AUTHOR CONTRIBUTIONS**

Conceptualization: Woo Sik Yu, Sun Mi Choi, Kyeongman Jeon, and Jin Gu Lee. Data curation: all authors. Formal analysis: Woo Sik Yu and Sun Mi Choi. Investigation: all authors. Methodology: Woo Sik Yu, Sun Mi Choi, Kyeongman Jeon, and Jin Gu Lee. Validation: Hye Ju Yeo, Dong Kyu Oh, Sung Yoon Lim, Young Tae Kim, Kyeongman Jeon, and Jin Gu Lee. Writing—original draft: Woo Sik Yu and Sun Mi Choi. Writing—review & editing: all authors. Approval of final manuscript: all authors.

## **ORCID iDs**

Woo Sik Yu Sun Mi Choi Hye Ju Yeo Dong Kyu Oh Sung Yoon Lim Young Tae Kim Kyeongman Jeon Jin Gu Lee https://orcid.org/0000-0002-5100-9131 https://orcid.org/0000-0002-0742-6085 https://orcid.org/0000-0002-8403-5790 https://orcid.org/0000-0002-7511-9634 https://orcid.org/0000-0003-3161-8711 https://orcid.org/0000-0001-9006-4881 https://orcid.org/0000-0002-4822-1772 https://orcid.org/0000-0003-2767-6505

- 1. Kotloff RM, Thabut G. Lung transplantation. Am J Respir Crit Care Med 2011;184:159-71.
- 2. National Institute of Organ, Tissue and Blood Management. Annual report of the transplant 2021 [accessed on 2023 May 1]. Available at: https://www.konos.go.kr/board/boardListPage. do?page=sub4\_2\_1&boardId=30.
- 3. Yu WS, Kim SY, Kim YT, Lee HJ, Park S, Choi SM, et al. Characteristics of lung allocation and outcomes of lung transplant according to the Korean urgency status. Yonsei Med J 2019;60:992-7.
- 4. Huh JW, Hong SB, Do KH, Koo HJ, Jang SJ, Lee MS, et al. Inhalation lung injury associated with humidifier disinfectants in adults. J Korean Med Sci 2016;31:1857-62.
- Yeo HJ, Oh DK, Yu WS, Choi SM, Jeon K, Ha M, et al. Outcomes of patients on the lung transplantation waitlist in Korea: a Korean network for organ sharing data analysis. J Korean Med Sci 2022; 37:e294.
- 6. Yeo HJ. Allocation of donor lungs in Korea. J Chest Surg 2022;55: 274-6.
- 7. Hoetzenecker K, Donahoe L, Yeung JC, Azad S, Fan E, Ferguson ND, et al. Extracorporeal life support as a bridge to lung transplantation-experience of a high-volume transplant center. J Thorac Cardiovasc Surg 2018;155:1316-28.E1.
- 8. Gottlieb J, Smits J, Schramm R, Langer F, Buhl R, Witt C, et al. Lung transplantation in Germany since the introduction of the lung allocation score. Dtsch Arztebl Int 2017;114:179-85.
- 9. Schechter MA, Ganapathi AM, Englum BR, Speicher PJ, Daneshmand MA, Davis RD, et al. Spontaneously breathing extracorporeal membrane oxygenation support provides the optimal bridge to lung transplantation. Transplantation 2016;100:2699-704.
- 10. Hayanga AJ, Aboagye J, Esper S, Shigemura N, Bermudez CA, D'Cunha J, et al. Extracorporeal membrane oxygenation as a bridge to lung transplantation in the United States: an evolving strategy in

the management of rapidly advancing pulmonary disease. J Thorac Cardiovasc Surg 2015;149:291-6.

ΥΜ

- 11. Egan TM, Murray S, Bustami RT, Shearon TH, McCullough KP, Edwards LB, et al. Development of the new lung allocation system in the United States. Am J Transplant 2006;6(5 Pt 2):1212-27.
- 12. Smits JM, Nossent G, Evrard P, Lang G, Knoop C, Kwakkel-van Erp JM, et al. Lung allocation score: the Eurotransplant model versus the revised US model a cross-sectional study. Transpl Int 2018; 31:930-7.
- 13. Yu WS, Suh JW, Song SH, Paik HC, Kim SY, Park MS, et al. The lung allocation score could evaluate allocation systems in countries that do not use the score. PLoS One 2019;14:e0214853.
- OPTN Executive Committee. Establish continuous distribution of lungs [accessed on 2023 May 1]. Available at: https://optn.transplant.hrsa.gov/media/b13dlep2/policy-notice\_lung\_continuousdistribution.pdf.
- 15. van der Mark SC, Hoek RAS, Hellemons ME. Developments in lung transplantation over the past decade. Eur Respir Rev 2020;29: 190132.
- Eurotransplant. LAS score: calculate [Internet] [accessed on 2021 November 1]. Available at: https://www.eurotransplant.org/lascalculator.
- 17. Pfister R, Schwarz KA, Janczyk M, Dale R, Freeman JB. Good things peak in pairs: a note on the bimodality coefficient. Front Psychol 2013;4:700.
- Hothorn T, Hornik K, Zeileis A. Unbiased recursive partitioning: a conditional inference framework. J Comput Graph Stat 2006;15: 651-74.
- 19. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol 1995;57:289-300.
- Egan TM, Edwards LB. Effect of the lung allocation score on lung transplantation in the United States. J Heart Lung Transplant 2016; 35:433-9.