Long- and short-term clinical impact of awake extracorporeal membrane oxygenation as bridging therapy for lung transplantation

Nam Eun Kim1,3, Ala Woo1, Song Yee Kim1, Ah Young Leem1, Youngmok Park1, Se Hyun Kwak1, Seung Hyun Yong1, Kyungsoo Chung1, Moo Suk Park1, Young Sam Kim1, Ha Eun Kim2, Jin Gu Lee2, Hyo Chae Paik2 and Su Hwan Lee1*

Abstract

Background: As lung transplantation (LTx) is becoming a standard treatment for end-stage lung disease, the use of bridging with extracorporeal membrane oxygenation (ECMO) is increasing. We examined the clinical impact of being awake during ECMO as bridging therapy in patients awaiting LTx.

Methods: In this single-center study, we retrospectively reviewed 241 consecutive LTx patients between October 2012 and March 2019; 64 patients received ECMO support while awaiting LTx. We divided into awake and non-awake groups and compared.

Results: Twenty-five patients (39.1%) were awake, and 39 (61.0%) were non-awake. The median age of awake patients was 59.0 (interquartile range, 52.5–63.0) years, and 80% of the group was men. The awake group had better post-operative outcomes than the non-awake group: statistically shorter post-operative intensive care unit length of stay [awake vs. non-awake, 6 (4–8.5) vs. 18 (11–36), \( p < 0.001 \)], longer ventilator free days [awake vs. non-awake, 24 (17–26) vs. 0 (0–15), \( p < 0.001 \)], and higher gait ability after LTx (awake vs. non-awake, 92% vs. 59%, \( p = 0.004 \)), leading to higher 6-month and 1-year lung function (forced expiratory volume in 1 s: awake vs. non-awake, 6-month, 77.5% vs. 61%, \( p = 0.004 \), 1-year, 75% vs. 57%, \( p = 0.013 \)). Furthermore, the awake group had significantly lower 6-month and 1-year mortality rates than the non-awake group (6-month 12% vs. 38.5%, \( p = 0.022 \), 1-year 24% vs. 53.8%, \( p = 0.018 \)).

Conclusions: In patients with end-stage lung disease, considering the long-term and short-term impacts, the awake ECMO strategy could be useful compared with the non-awake ECMO strategy.

Keywords: Extracorporeal membrane oxygenation, Lung transplantation, Critical care, Respiratory function tests

Background

Lung transplantation (LTx) is a final treatment option for patients with end-stage lung disease. Since the first successful LTx by Cooper and colleagues in 1983, the number of lung transplants has increased to up to 69,000 cases over the past 30 years. Most LTx are performed in patients with slowly progressive end-stage lung disease; however, some patients need bridging...
strategies due to acute or chronic respiratory failure [1–3].

These issues have increased the interest in bridging strategies for LTx candidates who become too sick to survive until an organ is available. Bridging with extracorporeal membrane oxygenation (ECMO) can reduce the risk of refractory hypercapnia or hypoxia requiring a mechanical ventilator [4]. However, it was contraindicated with LTx in the 1970s and 1980s because of poor perioperative outcomes and many complications [5, 6]. As the techniques and experiences related to ECMO improved, the literature on pre-transplant ECMO showed postoperative benefits in high-risk candidates; accordingly, the proportion of patients receiving bridging ECMO is increasing [7–11].

Furthermore, “awake ECMO” has been used for bridging. ECMO could replace a mechanical ventilator [12]. Such a strategy not only prevents complications related to mechanical ventilation, sedation, and immobilization, but also enables participation of pulmonary rehabilitation [12]. Consequently, it extends the candidacy of recipients and helps them maintain their physical condition whilst awaiting LTx [4, 13, 14]. However, the use of awake ECMO is associated with problems such as cannula displacement, patient discomfort, pain, and anxiety [12]. Our hospital initiated awake ECMO in 2015, and in this study, we evaluated the clinical impact of awake ECMO as a bridging therapy in patients awaiting LTx.

Methods
Study design and population
This was a retrospective, single-center, 7-year cohort study involving consecutive patients receiving LTx in South Korea between October 2012 and June 2019. During the study period, 241 patients received LTx. Fifteen patients were excluded for the following reasons: five patients were aged <18 years, five underwent co-transplantation of the lung and another organ, two underwent LTx with off-pump coronary artery bypass, two underwent re-transplantation, and one was transferred to our hospital after long-term ECMO care in other hospital (Fig. 1). A total of 64 were bridged ECMO, among them 25 were awake ECMO, and 39 were non-awake ECMO. We compared clinical impacts between two groups, in terms of short clinical course such as, ICU length of stay, ventilator free days, survival rates and long term effects such as lung function after lung transplantation, ability to walk, and also long term survival rate.

Data collection and definition
The data of the enrolled patients were collected from the electronic medical records of the hospital. Patient data, including demographic data, laboratory values,
comorbidities, and transthoracic echocardiogram (TTE) parameters before and after LTx, were collected. ECMO flow was detected at 24 h after cannulation. The severity of each patient’s condition when initiating ECMO therapy was calculated using the acute physiology and chronic health evaluation II (APACHE II) score within 24 h [15].

In our study, patients in the post-LTx period who could breathe for at least 24 h without assistance of a mechanical ventilator or home ventilator were regarded as having a ventilator-free status and ventilator-free days (VFDs) are calculated [16].

Physical activity during awake ECMO was measured according to our institutional pulmonary rehabilitation program. Two physical therapists examined the patients’ functional mobilization levels during awake ECMO, assessing step-by-step side rolling at the bedside, coming to a sitting position, from sitting up to standing, and standing unsupported if possible. Ambulation during ECMO was not allowed to prevent the risk of cannula-related complications and lack of manpower. Bedside physical therapy was provided to non-wake ECMO patients. In the post-transplantation period, pulmonary rehabilitation was applied to both awake and non-awake ECMO patients. Whether patients could walk and time to walking after LTx were investigated. During long-term follow-up, pulmonary function tests, including forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1), were investigated at 6 months and 1 year after LTx.

Bridging and awake ECMO
Most patients who need ECMO undergo a right jugular-femoral venous configuration (96.9%), and others (3.1%) done a femoral-femoral venous arterial configuration at the initial. After cannulation, sedative and analgesic drugs were tapered. If the patient was agitated, low dose dexmedetomidine was used to maintain a Richmond Agitation and Sedation Scale (RASS) score between 0 and 1 point. During waiting period, 4.7% were shifted to vena-arterial-venous cannulation according to parameters suggesting right heart failure such as increasing RVSP.

The patients underwent attempted extubation within 24–48 h after the initiation of ECMO if they had a stable gas exchange and hemodynamic status. If a difficult weaning process was predicted, early tracheostomy was performed within 48–72 h for a spontaneous breathing trial. The majority of the literature defines awake ECMO as liberation from invasive mechanical ventilation by extubation or early tracheostomy [4, 13, 14]. In our study, we defined awake ECMO as a state in which patients could maintain their awareness with an RASS score of 0–1 point, could breathe spontaneously, and could move their peripheral limbs such as foot or hand without ventilator support. However, some recipients could not wean from the mechanical ventilation but had alert consciousness and peripheral limb movement with the mechanical ventilator on continuous positive airway pressure (CPAP) or pressure support mode. These recipients were classified as non-awake in the first analysis and subclassified as tried awake ECMO in the subgroup analysis.

Additional ECMO management methods and postoperative immunosuppressive use are described in Additional file 3: Methods.

Statistical analyses
The SPSS software version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses; propensity score matching (PSM) was performed using the R program version 4.0.3 for Windows. Continuous variables were presented as medians (interquartile ranges [IQRs]) and categorical variables as numbers and percentages. The data were checked for normal distribution. Medians were analyzed using the Mann–Whitney U test for the awake and non-awake groups. Categorical variables were analyzed using the Chi-squared test or Fisher’s exact test. Kaplan–Meier statistics were used to estimate survival rates with statistical significance assessed by log rank analysis. To reduce the effect of APACHE II score and ECMO duration, PSM was used to match awake and non-awake ECMO patients. The Kruskal–Wallis test was used to investigate associations among the subgroups: non-awake, tried awake, and awake. For all analyses, p-values < 0.05 were considered statistically significant.

Results
Baseline characteristics of the patients receiving bridged ECMO according to the awake strategy
A total of 64 patients were treated with bridged ECMO; their median age was 56.5 (IQR, 49.3–62.8) years, and 41 (64.1%) patients were men. The major cause of LTx was idiopathic pulmonary fibrosis (n = 31, 48.4%), followed by connective tissue disease-associated interstitial lung disease (n = 11, 17.2%). Twenty-five patients (39.1%) underwent awake ECMO, and the proportion of patients has gradually increased over the past few years in our center (Additional file 1: Fig. S1). The 6-month and 1-year mortality rates of bridged ECMO patients were 28.1% (n = 18) and 42.2% (n = 27), respectively.

Table 1 shows the comparison between non-awake ECMO and awake ECMO patients. The APACHE II score at the time of ECMO initiation and proportion of female sex were significantly higher in the non-awake group than in the awake group. After LTx, the awake group had a significantly shorter median intensive care unit (ICU) length of stay and longer duration of VFDs than the
### Table 1  Baseline characteristics between non-awake ECMO and awake ECMO patients

|                          | Non-awake ECMO (n = 39) | Awake ECMO (n = 25) | p    |
|--------------------------|--------------------------|---------------------|------|
| Age, years               | 55 (49–62)               | 59 (52.5–63)        | 0.608|
| Male, sex                | 21 (53.8)                | 20 (80)             | 0.033|
| Donor age, years         | 45 (35–54.5)             | 43 (33–53)          | 0.650|
| Donor, male, sex         | 27 (69.2)                | 11 (44.0)           | 0.045|
| BMI, kg/m²               | 22.0 (19.0–25.3)         | 19.3 (16.8–23.2)    | 0.124|
| Primary lung disease     |                          |                     |      |
| IPF                      | 17 (43.6)                | 14 (56)             |      |
| AIP/ARDS                 | 4 (10.3)                 | 0 (0)               |      |
| CTD-related ILD          | 7 (17.9)                 | 4 (16)              |      |
| BO after PBSCT           | 1 (2.6)                  | 2 (8)               |      |
| Other                    | 10 (25.7)                | 5 (20)              |      |
| Hypertension             | 10 (25.6)                | 5 (20)              | 0.603|
| Diabetes mellitus        | 13 (33.3)                | 6 (24)              | 0.425|
| Pulmonary hypertension   | 22 (56.4)                | 12 (48)             | 0.511|
| Waiting list time, daysª | 14 (8–63.5)              | 87 (44–213)         | 0.001|
| TTE parameters before LTx|                          |                     |      |
| EF, %                    | 61 (56–68)               | 62 (55–68)          | 1    |
| E/E'                     | 10.4 (8–12)              | 10 (8.2–12)         | 0.75 |
| RVSP, mmHg               | 50 (30.8–64)             | 49 (37.5–53)        | 0.919|
| TAPSE, cm                | 1.9 (1.3–4.7)            | 1.8 (1.3–12)        | 1    |
| TDI                      | 12 (9–13)                | 11 (8.1–13.3)       | 0.647|
| APACHE II score          | 22 (18–28)               | 18 (13–19)          | 0.005|
| ECMO blood flow, mL      | 3170 (2880–3550)         | 3010 (2525–3575)    | 0.608|
| ECMO duration, days      | 12 (5–20)                | 13 (8–17)           | 0.841|
| ECMO configuration       |                          |                     |      |
| VV (jugular-femoral), %  | 37 (94.9)                | 25 (100)            |      |
| VA (femoral-femoral), %  | 2 (5.1)                  | 0 (0)               |      |
| Type of transplantation  |                          |                     | 0.420|
| Bilateral transplantation,%| 38 (97.4)               | 25 (100)            |      |
| Single transplantation, %| 1 (2.6)                  | 0 (0)               |      |
| Ischemia time, s         | 205 (1905–2740)          | 230 (192–265)       | 0.680|
| Post-transplant TTE parameters |                  |                     |      |
| EF, %                    | 62 (58–68)               | 65 (62–69.5)        | 0.257|
| E/E'                     | 11 (6.5–11.5)            | 9.5 (7–12.8)        | 0.289|
| RVSP, mmHg               | 27 (25–38)               | 34.5 (28.5–39)      | 0.55 |
| Ventilator free days     | 0 (0–15)                 | 24 (17–26)          | <0.001|
| Ability to gait after LTx| 23 (59)                  | 23 (92)             | 0.004|
| Time to gaiting, days    | 27.5 (18.5–37.5)         | 17 (10.0–29)        | 0.042|
| Three-months mortality   | 9 (23.1)                 | 1 (4)               | 0.074|
| Six-month mortality      | 15 (38.5)                | 3 (12)              | 0.022|
| One-year mortality       | 21 (53.8)                | 6 (24)              | 0.018|
| ICU length of stay, days | 18 (11–36)               | 6 (4–8.5)           | <0.001|
| Hospital length of stay, days | 61 (39–107)             | 36 (24–91)          | 0.061|
| Six-month FVC, % (14/18)*| 62 (50.5–67.8)           | 70 (59.5–78.5)      | 0.059|
| Six-month FEV1, % (14/18)*| 61 (41.5–73.3)           | 77.5 (69–96.5)      | 0.004|
| One-year FVC, % (15/18)* | 63 (53–69)               | 71 (62.8–79.3)      | 0.04 |
| One-year FEV1, % (15/18)*| 57 (49–70)               | 75 (61.5–96.8)      | 0.013|

Data are presented as numbers (percentages) or medians (interquartile range).

ECMO extracorporeal membrane oxygenation, BMI body mass index, IPF idiopathic pulmonary fibrosis, AIP acute interstitial pneumonia, ARDS acute respiratory distress syndrome, CTD connective tissue disease, BO after PBSCT bronchiolitis obliterans after peripheral blood stem cell transplantation, TTE transthoracic echocardiography, LTx lung transplantation, EF ejection fraction, E/E' ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity, RVSP right ventricular systolic pressure
non-awake group (ICU length of stay, 6 vs. 18, *p* < 0.001; VFDs, 24 vs. 0, *p* < 0.001). In addition, more patients were able to walk after LTx in the awake group than in the non-awake group (92% vs. 59%, *p* = 0.004).

The 1-year mortality rate of the awake group was significantly lower in the awake group than in the non-awake group (24% vs. 53.8%, *p* = 0.018). In survivors, both the FVC and FEV₁ measured at 6 months and 1 year were significantly higher in the awake group than in the non-awake group (6-month FEV₁, 77.5% vs. 61%, *p* = 0.004; 1-year FEV₁, 75% vs. 57%, *p* = 0.013). In the overall Kaplan–Meier survival analysis, the awake group showed a significantly higher survival rate than the non-awake group (*p* = 0.011, Fig. 2A).

### Comparison of the non-awake and awake ECMO groups after propensity score matching of the APACHE II score and ECMO duration

Because the severity of patient condition and ECMO duration may affect the results of analysis, PSM was used to match the severity score and ECMO duration of awake and non-awake ECMO patients (Additional file 1: Fig. S2). Table 2 shows the results of comparison between non-awake ECMO and awake ECMO patients after PSM of the APACHE II score and ECMO duration. There was a statistically significant difference in VFDs, ICU length of stay, and ability to walk after LTx between the groups (awake vs. non-awake, respectively, VFD, 24 vs. 0, *p* < 0.001; ICU length of stay, 6 vs. 13, *p* = 0.001; ability to walk 92% vs. 56%, *p* = 0.004). Although there was no significant difference in the 1-year mortality rate and survival analysis results between the awake and non-awake groups, lung function parameters, including 6-month and 1-year FVC and FEV₁, were significantly higher in the awake group than in the non-awake group (6-month FEV₁ 77.5% vs. 58%, *p* = 0.001; 1-year FEV₁ 75% vs. 56.5%, *p* < 0.001).

### Subgroup analysis of postoperative outcome and survival in awake patients according to mechanical ventilator support

In some recipients, awake ECMO was tried, although ventilator withdrawal was unsuccessful, and spontaneous breathing was maintained with CPAP or pressure support mode. These recipients were defined as the tried ECMO group and compared with the absolutely non-awake and awake groups. Eight patients were awake with spontaneous breathing via CPAP or pressure support mode. Table 3 shows the results of subgroup analysis. Before LTx, there was no significant difference in age, cause of LTx, comorbidities, TTE parameters, and ECMO durations among the groups. However, the APACHE II score showed significant differences among the groups (*p* = 0.003). The APACHE II score was statistically higher in the tried awake ECMO group than in the awake group (tried awake vs. awake, 21 vs. 26, *p* = 0.002). After LTx, there was a significant difference in VFDs (*p* < 0.001), ability to walk (*p* = 0.009), ICU length of stay (*p* < 0.001),

---

**Table 1** (continued)

| Ventricular systolic pressure, TAPSE tricuspid annular plane systolic excursion, TDI tissue Doppler imaging, APACHE acute physiology and chronic health evaluation, ICU intensive care unit, FVC forced vital capacity, FEV₁ forced expiratory volume in 1 s |
|Waiting list time after Korean Network for Organ Sharing registration |

---

**Fig. 2** Kaplan–Meier survival curves of bridged ECMO patients according to the awake strategy. **A** Overall survival rate between the awake and non-awake groups in the total study population. **B** Overall survival rate between the awake and non-awake groups after propensity score matching of the APACHE II score and ECMO duration.
and length of hospital stay ($p = 0.043$) among the groups. Furthermore, for survivors, the 6-month FVC and FEV$_1$ were significantly different among the groups (FVC, $p = 0.045$, FEV$_1$, $p = 0.011$). The awake group had significantly higher 6-month FVC and FEV$_1$ than the absolutely non-awake group ($p = 0.018$, $p = 0.003$, Fig. 3), and there was no difference between the awake and tried awake groups ($p = 0.854$, Fig. 3).

## Discussion

In this study, we investigated the post-operative outcomes of patients with end-stage respiratory disease, who inevitably need bridging ECMO during the waiting time, and the clinical impact of being awake during ECMO apply. In our investigation, the awake strategy could

| Table 2 | Comparison between non-awake ECMO and awake ECMO patients after propensity score matching of the APACHE II score and ECMO duration |
|---------|---------------------------------------------------------------------------------------------------------------|
|         | Non-awake ECMO (n = 25)                                                                                       | Awake ECMO (n = 25)                                           | $p$   |
| Age, years | 54 (48.5–59)                                                                                                 | 59 (52.5–63)                                                  | 0.084 |
| Male, sex  | 11 (44)                                                                                                       | 20 (80)                                                      | 0.009 |
| BMI, kg/m$^2$ | 21.3 (19.1–25.2)                                                                                              | 19.3 (16.8–23.2)                                             | 0.16  |
| Primary lung disease |                                                                                                                                                   | 0.059 |
| IPF       | 7 (28)                                                                                                        | 14 (56)                                                      | 0.808 |
| AIP/ARDS  | 3 (12)                                                                                                        | 0 (0)                                                        | 0.856 |
| CTD-related ILD | 6 (24)                                                                                       | 4 (16)                                                      | 0.453 |
| BO after PBSCT | 1 (4)                                                                                              | 2 (8)                                                        | 0.117 |
| Other     | 7 (32)                                                                                                        | 5 (20)                                                       | 0.117 |
| Hypertension | 5 (20)                                                                                           | 5 (20)                                                      | 1     |
| Diabetes mellitus | 8 (32)                                                                                             | 6 (24)                                                      | 0.529 |
| Pulmonary hypertension | 13 (52)                                                                                          | 12 (48)                                                      | 0.777 |
| TTE parameters before LTx |                                                                                                                                                  | 0.001 |
| EF, %     | 61 (56–69)                                                                                                   | 62 (55–68)                                                   | 0.808 |
| E/E'      | 10 (8–11.5)                                                                                                   | 10 (8.2–12)                                                  | 0.856 |
| RVSP, mmHg | 45 (27.9–54)                                                                                                 | 49 (37.5–53)                                                 | 0.453 |
| APACHE II score, | 20 (14–22)                                                                                                | 18 (13–19)                                                   | 0.117 |
| ECMO blood flow, mL | 3140 (2940–3400)                                              | 3010 (2525–3575)                                             | 0.479 |
| ECMO duration, days | 11 (8–19.5)                                                          | 13 (8–17)                                                   | 0.904 |
| Ventilator free days | 0 (0–20)                                             | 24 (17–26)                                                  | <0.001|
| Ability to gait after LTx | 14 (56)                                                                  | 23 (92)                                                     | 0.004 |
| Time to gaiting, days | 22 (10–33)                                                        | 17 (10–29)                                                  | 0.248 |
| Three-month mortality | 6 (24)                                                                    | 1 (4)                                                       | 0.098 |
| Six-month mortality | 8 (32)                                                                     | 3 (12)                                                      | 0.088 |
| One-year mortality | 12 (48)                                                                   | 6 (24)                                                      | 0.077 |
| ICU length of stay, days | 13 (6.5–24.5)                                                   | 6 (4–8.5)                                                    | 0.001 |
| Hospital length of stay, days | 51 (36–90)                                                       | 36 (24–91)                                                   | 0.327 |
| Six-month FVC, % (10/18)* | 61.5 (50.5–66.3)                                      | 70 (59.5–78.5)                                               | 0.031 |
| Six-month FEV$_1$, % (10/18)* | 58 (41.5–66)                                        | 77.5 (69–96.5)                                               | 0.001 |
| One-year FVC, % (12/18)* | 60.5 (53–65)                                                      | 71 (62.8–79.3)                                               | 0.009 |
| One-year FEV$_1$, % (12/18)* | 56.5 (45.3–60.5)                                                                 | 75 (61.5–96.8)                                               | <0.001|

Data are presented as numbers (percentages) or medians (interquartile ranges).

ECMO extracorporeal membrane oxygenation, APACHE acute physiology and chronic health evaluation, BMI body mass index, IPF idiopathic pulmonary fibrosis, AIP acute interstitial pneumonia, ARDS acute respiratory distress syndrome, CTD connective tissue disease, BO after PBSCT bronchiolitis obliterans after peripheral blood stem cell transplantation, TTE transthoracic echocardiography, LTx lung transplantation, EF ejection fraction, $E’/E$ ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity, RVSP right ventricular systolic pressure, ICU intensive care unit, FVC forced vital capacity, FEV$_1$ forced expiratory volume in 1 s, APACHE II Acute Physiologic Assessment and Chronic Health Evaluation II

*Number of patients included in pulmonary function analysis
increase the VFDs and decrease ICU length of stay after LTx compared with the non-awake strategy. On long-term follow-up, we found that the awake group showed higher gait ability and higher lung function, such as FVC and FEV1, than the non-awake group; the former showed a significantly higher overall survival rate than the latter.

Immobility due to critical illness leads to decreased muscle protein synthesis and increased muscle catabolism, leading to decreased muscle mass [17]. This can lead to a pro-inflammatory state, increasing the proportion of reactive oxygen species that induce the oxygenation of myofilaments, resulting in contractile dysfunction and muscle atrophy [18, 19]. Immunosuppression therapy could delay the recovery of quadriceps strength, making it difficult for the patients to reach their pre-operative physical condition [20]. Awake ECMO while awaiting LTx could eliminate sedation and help avoid prolonged immobilization and facilitate pulmonary rehabilitation. Maintaining respiratory muscle tone and preventing diaphragm atrophy could help ventilation to even dependent

Table 3 Comparison among non-awake ECMO, tried ECMO, and awake ECMO patients

|                      | Absolutely non-awake ECMO (n = 31) | Tried awake ECMO (n = 8) | Awake ECMO (n = 25) | p     |
|----------------------|------------------------------------|--------------------------|---------------------|-------|
| Age, years           | 54 (49–59)                         | 59.5 (54.5–62.8)         | 59 (52.5–63)        | 0.148 |
| Male, sex            | 15 (48.4)                          | 6 (75)                   | 20 (80)             | 0.043 |
| BMI, kg/m²           | 21.5 (18.5–25.1)                   | 22.4 (20.7–26.0)         | 19.3 (16.8–23.2)    | 0.173 |
| Primary lung disease |                                    |                          |                     | 0.404 |
| IPF                  | 13 (41.9)                          | 4 (50)                   | 14 (56)             |       |
| AIP/ARDS             | 4 (12.9)                           | 0 (0)                    | 0 (0)               |       |
| CTD-related ILD      | 4 (12.9)                           | 3 (37.5)                 | 4 (16)              |       |
| BO after PBSCT       | 1 (3.2)                            | 0 (0)                    | 2 (8)               |       |
| Other                | 9 (29)                             | 1 (12.5)                 | 5 (20)              |       |
| Hypertension         | 9 (29)                             | 1 (12.5)                 | 5 (20)              | 0.649 |
| Diabetes mellitus    | 9 (31)                             | 4 (50)                   | 6 (24)              | 0.381 |
| Pulmonary hypertension| 17 (54.8)                         | 5 (62.5)                 | 12 (48)             | 0.829 |
| TTE parameters before LTx |                          |                          |                     |       |
| EF, %                | 61 (56–66)                         | 67 (58.3–75.3)           | 62 (55–68)          | 0.286 |
| E/E’                 | 11 (8–12)                          | 9 (6.9–12.5)             | 10 (8.2–12)         | 0.725 |
| RVSP, mmHg           | 48 (30.8–61)                       | 58 (32.3–60.3)           | 49 (37.5–53)        | 0.493 |
| APACHE II score      | 21 (17–28)                         | 26 (21.5–28.8)           | 18 (13–19)          | 0.003 |
| ECMO blood flow, mL  | 3170 (2750–3550)                   | 3270 (3100–3560)         | 3010 (2525–3757)    | 0.443 |
| ECMO duration, days  | 10 (4–19)                          | 17.5 (9.5–26.5)          | 13 (8–17)           | 0.277 |
| Ventilator free days | 0 (0–20)                           | 5 (0–17)                 | 24 (17–26)          | <0.001|
| Three-month mortality| 7 (22.6)                           | 2 (25)                   | 1 (4)               | 0.085 |
| Six-month mortality  | 12 (38.7)                          | 3 (37.5)                 | 3 (12)              | 0.049 |
| One-year mortality   | 16 (51.6)                          | 5 (62.5)                 | 6 (24)              | 0.053 |
| Ability to gait after LTx | 18 (58.1)                     | 5 (62.5)                 | 23 (92)             | 0.009 |
| Time to gaiting, days| 27 (18–33)                         | 28 (21–47)               | 17 (10–29)          | 0.089 |
| ICU length of stay, days | 18 (11–37)                         | 16 (9.8–31.8)            | 6 (4.8–5)           | <0.001|
| Hospital length of stay, days | 51 (38–92)                | 85 (58.8–173.8)          | 36 (24–91)          | 0.043 |
| Six-month FVC, % (11/3/18)* | 61 (49–65)            | 70 (68.5–70.5)           | 70 (59.5–78.5)      | 0.045 |
| Six-month FEV1, % (11/3/18)* | 56 (40–64)          | 72 (72–72.5)             | 77.5 (69–96.5)      | 0.011 |
| One-year FVC, % (12/3/18)* | 61 (53–68)            | 65 (63.5–83.5)           | 71 (62.8–79.3)      | 0.056 |
| One-year FEV1, % (12/3/18)* | 57 (45.3–67.8)        | 70 (63–92.5)             | 75 (61.5–96.8)      | 0.017 |

Data are presented as numbers (percentages) or medians (interquartile ranges)

ECMO extracorporeal membrane oxygenation, BMI body mass index, IPF idiopathic pulmonary fibrosis, AIP acute interstitial pneumonia, ARDS acute respiratory distress syndrome, CTD connective tissue disease, BO after PBSCT bronchiolitis obliterans after peripheral blood stem cell transplantation, TTE transthoracic echocardiography, LTx lung transplantation, EF ejection fraction, E/E’ ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity, RVSP right ventricular systolic pressure, APACHE acute physiology and chronic health evaluation, ICU intensive care unit, FVC forced vital capacity, FEV1 forced expiratory volume in 1 s

*Number of patients included in pulmonary function analysis
We supposed that these effects might help increase VFDs and gait ability after LTx. Furthermore, awake patients with spontaneous breathing can move their diaphragm, and this can prevent muscle atrophy [21]. Although some patients in the awake group failed to withdraw from the mechanical ventilator, the lung function (FVC and FEV₁) of patients who maintained spontaneous breathing showed a higher tendency to improvement than that of patients in the absolutely non-awake group (Fig. 3). Furthermore, even after adjusting for severity using propensity score matching, the lung function (FVC and FEV₁) of the awake group was higher than that of the non-awake group. Goligher et al. reported that diaphragm atrophy and decreased muscle thickness during mechanical ventilation were associated with low rates of independence from ventilator support [22]. Previous studies have reported that the awake strategy could minimize ICU-related complications associated with sedation, delirium, and critical illness myopathy [12, 23, 24]. In our study, these effects of awake ECMO and increased VFDs contributed to the short lengths of ICU stay in this group.

However, the survival rates in our study were lower than those in previous studies, reaching up to 80% [4, 14, 25]. This could be explained by the different organ allocation systems of different governments, lack of dual-lumen single cannulas in South Korea, and strict de-listing criteria in the waiting period of other centers. In the Columbia group, strict de-listing criteria during waiting time was observed. In their study, among 72 patients who received awake ECMO, 55.6% patients who were able to walk in a good condition received LTx, and other patients were de-listed because of scarce resources [14]. Most countries use lung allocation scores or priority organ allocation systems based on a combination of wait-list urgency and the probability of post-transplant survival. However, in South Korea, the priority of the organ allocation system of the government is predominantly determined by the emergency of a patient’s status, and this is justified by ethical principles [26]. For these reason, the percentage of patients requiring ECMO bridge to LTx is high, up to 26.5%. And it is hard to make a decision of de-listing of the severity status of bridged patients according to efficacy. Therefore, our cohort probably include bridged ECMO patients for whom good prognosis was not expected, and LTx was performed due to ethical priority. Further, the cannulation technique in our study was different from that used in other studies. In the Cleveland group, advances in cannula design that facilitate gait (double-lumen single cannula) were used, and

![Fig. 3 Six-month and 1-year lung function after lung transplantation](image-url)
the cannulas were positioned in the upper extremities to help restore gait subsequently; in their cohort, 26% (5 of 19) of the patients could successfully walk during awake ECMO [27]. Unfortunately, since double-lumen single catheters are not available in South Korea, which may have interfered with rehabilitation during awake ECMO. These different social, environment circumstances during the waiting period and retrospective observational study design in a single tertiary center in Asia could be the limitations in our study compared with previous studies in North America or Europe. However, since many studies on awake ECMO for LTx were performed in North America or Europe, this study will provide helpful data for patients awaiting LTx in Asia. Furthermore, our study showed that awake ECMO could improve long-term lung function, including FVC and FEV1. To the best of our knowledge, there are few reports of long-term lung function after LTx using awake ECMO, and our results may be helpful for researchers attempting awake ECMO.

Conclusions
For patients with end-stage lung disease, considering the long-term and short-term impacts such as VFDs, ICU length of stay, mortality, and lung function, the awake ECMO strategy could be useful compared with the non-awake ECMO strategy.

Abbreviations
ECMO: Extracorporeal membrane oxygenation; BMI: Body mass index; LTx: Lung transplantation; APACHE: Acute physiology and chronic health evaluation; ICU: Intensive care unit; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 s.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12931-021-01905-7.

Additional file 1: Figure S1. Percentage of awake ECMO bridging in the hospital. The incidence of bridging ECMO has increased up to 20% in lung transplant recipients since 2017; the proportion of awake ECMO is rapidly increasing.

Additional file 2: Figure S2. Distribution of propensity score.

Additional file 3. Supplementary material, methods.

Acknowledgements
We thank for dedication for excellent lung transplantation team.

Authors’ contributions
Conceptualization: NEK, AW, SYK, AYL, SHK, SHY, KC, MSP, YSK, HEK, JGL, HCP, SHL. Data curation: NEK, HEK. Formal analysis: NEK, SHL. Investigation: NEK, SHL. Methodology: NEK, SHL. Supervision: AW, SYK, AYL, KC, MSP, YSK, JGL, HCP, SHL. Validation: MSP, SHL. Writing – original draft: NEK. Writing-review and editing: NEK, MSP, SHL. All authors read and approved the final manuscript.

Funding
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (Grant number: NRF-2018R1C1B6004282). In addition, this work was supported by the Korea Medical Device Development Fund grant funded by the Korea government (the Ministry of Science and ICT, the Ministry of Trade, Industry and Energy, the Ministry of Health & Welfare, the Ministry of Food and Drug Safety) (project number: 2020011926).

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
The study protocol was approved by the institutional review board of Severance Hospital (approval no.: 4-2019-1294). This study adhered to the principles of the Declaration of Helsinki (2000) and Declaration of Istanbul (2008).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests that could have influenced the present study.

Author details
1 Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1, Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea. 2 Department of Thoracic and Cardiovascular Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea. 3 Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Ewha Womans University College of Medicine, Ewha Womans Seoul Hospital, Seoul, South Korea.

Received: 12 September 2021 Accepted: 23 November 2021

References
1. Shah PD, Orens JB. Guidelines for the selection of lung-transplant candidates. Curr Opin Organ Transplant. 2012;17:467–73.
2. Mattar A, Chatterjee S, Loo C. Bridging to lung transplantation. Crit Care Clin. 2019;35:11–25.
3. Cooper JD, Pearson FG, Patterson GA, Todd TR, Ginesson RJ, Goldberg M, DeMajo WA. Technique of successful lung transplantation in humans. J Thorac Cardiovasc Surg. 1987;93:173–81.
4. Fuehner T, Kuehn C, Hadem J, Wiener G, Gottlieb J, Tudorache I, Olsson KM, Greer M, Sommer W, Weite T, et al. Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. Am J Respir Crit Care Med. 2012;185:763–8.
5. Maurer JR, Frost AE, Estenne M, Higenbottam T, Glanville AR. International guidelines for the selection of lung transplant candidates. The International Society for Heart and Lung Transplantation, the American Thoracic Society, the American Society of Transplant Physicians, the European Respiratory Society. Transplantation. 1998;66:951–6.
6. Jurmann MJ, Schaefers DJ, Demertzis S, Haverich A, Wahlers T, Borst HG. Emergency lung transplantation after extracorporeal membrane oxygenation. Asaio J. 1993;39:M448-452.
7. George Tj, Beaty CA, Kicic A, Shah PD, Merlo CA, Shah AS. Outcomes and temporal trends among high-risk patients after lung transplantation in the United States. J Heart Lung Transplant. 2012;31:1182–91.
8. Toyoda Y, Bhamka JK, Shimamura N, Zaldonis D, Pilewski J, Crespo M, Bermudez C. Efficacy of extracorporeal membrane oxygenation as a bridge to lung transplantation. J Thorac Cardiovasc Surg. 2013;145:1065–71.
9. Cypel M, Keshavjee S. Extracorporeal life support as a bridge to lung transplantation. Clin Chest Med. 2011;32:245–51.
10. Lafarge M, Mordant P, Thabut G, Brouchet L, Falcoz PE, Haloun A, Le Pimpec-Barthes F, Mary JM, Reynaud-Gaubert M, Saint-Raymond C, et al. Experience of extracorporeal membrane oxygenation as a bridge to lung transplantation in France. J Heart Lung Transplant. 2013;32:905–13.
11. Benazzo A, Schwarz S, Frommlet F, Schweiger T, Jakisch P, Schellongowski P, Staudinger T, Klepertko W, Lang G, Hoetzenecker K. Twenty-year experience with extracorporeal life support as bridge to lung transplantation. J Thorac Cardiovasc Surg. 2019;157:2515-2525.e2510.

12. Langer T, Santini A, Bottino N, Crotti S, Batchinsky AI, Pesenti A, Gattinoni L. "Awake" extracorporeal membrane oxygenation (ECMO): pathophysiology, technical considerations, and clinical pioneering. Crit Care. 2016;20:150.

13. Ko Y, Cho YH, Park YH, Lee H, Suh GY, Yang JH, Park CM, Jeon K, Chung CR. Feasibility and safety of early physical therapy and active mobilization for patients on extracorporeal membrane oxygenation. Asaio J. 2015;61:564–8.

14. Biscotti M, Gannon WD, Agerstrand C, Abrams D, Sonett J, Brodie D, Bacchetta M. Awake extracorporeal membrane oxygenation as bridge to lung transplantation: a 9-year experience. Ann Thorac Surg. 2017;104:412–9.

15. Knauert WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13:818–29.

16. Contentin L, Ehrmann S, Giraudieu B. Heterogeneity in the definition of mechanical ventilation duration and ventilator-free days. Am J Respir Crit Care Med. 2014;189:998–1002.

17. Kortebein P, Fernando A, Lombeida J, Wolfe R, Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. JAMA. 2007;297:1772–4.

18. Truong AD, Fan E, Brower RG, Needham DM. Bench-to-bedside review: mobilizing patients in the intensive care unit—from pathophysiology to clinical trials. Crit Care. 2009;13:216.

19. Andrade FH, Reid MB, Allen DG, Westerblad H. Effect of hydrogen peroxide and dithiothreitol on contractile function of single skeletal muscle fibres from the mouse. J Physiol. 1998;509(Pt 2):565–75.

20. Pehlivan E, Mutluay F, Balci A, Kilic L. The effects of inspiratory muscle training on exercise capacity, dyspnea and respiratory functions in lung transplantation candidates: a randomized controlled trial. Clin Rehabil. 2018;32:1328–39.

21. Yoshida T, Amato M, Kavanagh BP, Fujino Y. Impact of spontaneous breathing during mechanical ventilation in acute respiratory distress syndrome. Curr Opin Crit Care. 2019;25:192–8.

22. Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, Vorona S, Sklar MC, Rittayamai N, Lanys A, et al. Mechanical ventilation-induced diaphragm atrophy strongly impacts clinical outcomes. Am J Respir Crit Care Med. 2018;197:204–13.

23. Lehr CJ, Zaas DW, Cheifetz IM, Turner DA. Ambulatory extracorporeal membrane oxygenation as a bridge to lung transplantation: walking while waiting. Chest. 2015;147:1213–8.

24. Stahl K, Seelig R, Hooper MM, David S. "Better be awake": a role for awake extracorporeal membrane oxygenation in acute respiratory distress syndrome due to Pneumocystis pneumonia. Crit Care. 2019;23:418.

25. Crotti S, Bottino N, Spinelli E. Spontaneous breathing during veno-venous extracorporeal membrane oxygenation. J Thorac Dis. 2018;10:5661–6669.

26. Lee JG, Park MS, Jeong SJ, Kim SY, Na S, Kim J, Palk HC. Critical care before lung transplantation. Acute Crit Care. 2018;33:197–205.

27. Hakim AH, Ahmad U, McCurry KR, Johnston DR, Petterson GB, Budev M, Murthy S, Blackstone EH, Tong MZ. Contemporary outcomes of extracorporeal membrane oxygenation used as bridge to lung transplantation. Ann Thorac Surg. 2018;106:182–8.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.