Received: 30 November 2020 | Revised: 29 June 2021 | Accepted: 30 June 2021

DOI: 10.1111/ajt.16759

ORIGINAL ARTICLE

Lung transplantation for acute respiratory distress syndrome: A multicenter experience

Anna E. Frick[1,2] | Christiaan T. Gan[3] | Robin Vos[4,5] | Stefan Schwarz[1] | Felix Kraft[6] | Daria Kifjak[7] | Arne P. Neyrinck[2] | Dirk E. Van Raemdonck[4,8] | Walter Klepetko[1] | Peter Jaksch[1] | Erik A. M. Verschuuren[3] | Konrad Hoetzenecker[1]

[1]Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria

[2]Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium

[3]Department of Pulmonary Diseases, University Medical Centre Groningen, Groningen, The Netherlands

[4]BREATHE, Leuven Lung Transplant Unit, Department of Chronic Diseases, Metabolism and Ageing (Chromed), KU Leuven, Leuven, Belgium

[5]Department of Respiratory Diseases, University Hospitals Leuven, Leuven, Belgium

[6]Department of Anaesthesia, General Intensive Care and Pain Management, Medical University of Vienna, Vienna, Austria

[7]Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Vienna, Austria

[8]Department of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium

Correspondence
Konrad Hoetzenecker, Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria.
Email: konrad.hoetzenecker@meduniwien.ac.at

Acute respiratory distress syndrome (ARDS) is a rapidly progressive lung disease with a high mortality rate. Although lung transplantation (LTx) is a well-established treatment for a variety of chronic pulmonary diseases, LTx for acute lung failure (due to ARDS) remains controversial. We reviewed posttransplant outcome of ARDS patients from three high-volume European transplant centers. Demographics and clinical data were collected and analyzed. Viral infection was the main reason for ARDS (n = 7/13, 53.8%). All patients were admitted to ICU and required mechanical ventilation, 11/13 were supported with ECMO at the time of listing. They were granted a median LAS of 76 (IQR 50–85) and waited for a median of 3 days (IQR 1.5–14). Postoperatively, median length of mechanical ventilation was 33 days (IQR 17–52.5), median length of ICU and hospital stay were 39 days (IQR 19.5–58.5) and 54 days (IQR 43.5–127). Prolongation of peripheral postoperative ECMO was required in 7/13 (53.8%) patients with a median duration of 2 days (IQR 2–7). 30-day mortality was 7.7%, 1 and 5-year survival rates were calculated as 71.6% and 54.2%, respectively. Given the lack of alternative treatment options, the herein presented results support the concept of offering live-saving LTx to carefully selected ARDS patients.

KEYWORDS
clinical research/practice, health services and outcomes research, lung (allograft) function/dysfunction, lung failure/injury, lung transplantation/pulmonology

Abbreviations: AMR, antibody-mediated rejection; ARDS, acute respiratory distress syndrome; ATG, antithymocyte globulin; BAL, broncho-alveolar lavage; CPB, cardiopulmonary bypass; DBD, donation after brain-stem death; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; eLAS, exceptional lung allograft score; ET, eurotransplant; FFP, fresh frozen plasma; ICU, intensive care unit; IRB, Institutional Review Board; LAS, lung allocation score; LTx, lung transplantation; MOF, multi organ failure; MRGN, multidrug-resistant gram-negative; PGD, primary graft dysfunction; pRBC, packed red blood cell; RA/PA, right atrium/pulmonary artery; RRT, renal replacement therapy; SAH, subarachnoid hemorrhage.

1 | INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a devastating clinical condition associated with a high mortality.[1] Current treatment strategies for ARDS mainly comprise supportive measures aiming to improve gas exchange and to prevent complications such as sepsis, kidney failure, bleeding, and thromboembolic events. These measures include protective lung ventilation, prone positioning, inhaled nitric oxide, surfactant replacement therapy, glucocorticoids, anti-inflammatory agents, and early implementation of extracorporeal membrane oxygenation (ECMO).[2–5]

Lung transplantation (LTx) is an established therapy for patients with end-stage chronic lung diseases. However, for acute lung failure, the evidence for LTx is limited to a few case reports.[6–19] To date, the only larger case series of LTx for ARDS was published in 2014 by a South Korean LTx center. This study included nine patients with a median posttransplant survival of 64 months. The authors concluded that LTx can be considered for a selected group of patients with severe ARDS.[20] In Europe and North America, LTx for acute lung failure is not routinely performed based on an international consensus, which is currently being challenged by the ongoing COVID-19 pandemic.[14] Consequently, selection criteria for offering this treatment to patients remain unclear.

We therefore sought to summarize the institutional experience of three European high-volume centers with LTx for ARDS, putting special emphasis on patient selection criteria, perioperative challenges and posttransplant outcome.

2 | METHODS

2.1 | Study design

This retrospective, multicenter cohort study included three European high-volume lung transplantation centers (Medical University of Vienna, Austria, University Hospitals Leuven, Belgium and the University Medical Centre Groningen, The Netherlands). All ARDS patients who received a lung transplantation between August 1998 and May 2020, were identified. The study protocol was approved by the Institutional Review Board (IRB) of each representative institution. The need for informed consent was waived due to the retrospective nature of the study (1973/2020, S51577, NCT03272841). ARDS was defined based on the Berlin criteria.[1] Patients with acute exacerbation of an idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD) or cystic fibrosis (CF) were excluded from the study. Also, chronic post-ARDS fibrosis as the indication for LTx was excluded. ARDS patients listed for LTx but not transplanted, were not analyzed. Demographic and clinical data were retrieved from the Eurotransplant (ET) database (donor) and from the respective institutional transplant databases (recipients).

PGD scores were calculated according to the latest ISHLT consensus[21] and were assessed retrospectively by chest X-rays and arterial blood gas analyses at the time of admission to the intensive care unit (ICU) 24, 48, and 72 h after LTx. Patients on prolonged postoperative ECMO were classified as PGD3 if chest X-rays showed bilateral infiltrations. In case of clear radiographs, prolonged ECMO patients were classified as "ungradable".

2.2 | Statistical analysis

All statistical analyses were performed using GraphPad Prism 8.0 (GraphPad Software). $p \leq .05$ were considered significant. Continuous data are presented as mean plus standard deviation when normally distributed, or median with interquartile range when non–normally distributed. For survival analysis, IBM SPSS Statistics version 26.0 (IBM) and Kaplan–Meier curve was used.

3 | RESULTS

3.1 | Recipient selection and listing

A total of 13 ARDS patients were transplanted during the study period. The main reason for acute lung failure was a viral infection (H1N1, cytomegalovirus, H3N1, and Covid-19; $n = 7$, 53.8%). Bacterial pneumonia resulting in ARDS, was documented in 5 (38.5%) patients. This was exclusively diagnosed in broncho-alveolar lavage (BAL) fluid cultures and included infection with *Legionella pneumophilia*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and multidrug-resistant gram-negative (MRGN) bacteria. One patient was diagnosed with systemic inflammatory response syndrome-induced ARDS after abdominal surgery with no clear evidence of a bacterial or viral infection (Table 1).

All 13 patients had been physically active before they were admitted to the hospital. They also had an unremarkable medical history. Due to the severity of their condition, none of the patients could be bridged awake to their transplant and patients were not able to participate in physiotherapy while being on ECMO.

At the time patients were first seen by the LTx team, the mean time on mechanical ventilation had been 43 days (IQR 34–56.5) and a tracheostomy had been placed in six patients (46.2%). Eleven (84.6%) patients were supported with ECMO with a median of 35 days (IQR 16–42.5). The most common type was a peripheral veno-venous ECMO (VV-ECMO)—9 patients (69.2%) were bridged with a femoral-jugular ECMO and one patient with a jugular double-lumen cannula. In one pediatric patient a central right atrium/pulmonary artery (RA/PA) ECMO was used. None of the patients could be bridged awake to their transplant and were not able to participate in physiotherapy while being on ECMO. All patients received a deep sedation and adequate analgesic therapy. Prolonged muscle relaxants/paralytics were not used. Three patients had required renal replacement therapy before but had completely recovered their kidney function at the time of listing. Seven out of 13 patients had a mild/moderate liver dysfunction with elevated liver enzymes but intact coagulation.

TABLE 1 Recipient characteristics

Number of patients	13
Recipient	
Age, years	29.2 (±3.6)
Gender, female (%)	8 (61.5)
BMI	23.1 (±1.2)
Underlying disease, *n* (%)	
Cytomegalovirus	1 (7.7)
H1N1 influenza	4 (30.8)
H3N1 influenza	1 (7.7)
Covid-19 infection	1 (7.7)
ARDS after abdominal sepsis	1 (7.7)
Pneumonia	5 (38.5)
At time of listing	
MV, *n* (%)	13 (100)
MV, days	43 (34–56.5)
ECLS support, *n* (%)	11 (84.6)
ECLS support, days	35 (16–42.5)
ECLS cannulation type	
Veno-venous peripheral	10 (76.9)
-Central RA/PA	1 (7.7)
ICU stay, days	44 (22–52)
LAS	76 (50–85)
Kidney parameters	
Creatinine, mg/dl	0.54 (0.3–0.9)
BUN, mg/dl	8.6 (6.2–13.9)
eGFR ml/min	
>60, *n* (%)	8 (61.5)
40–60, *n* (%)	5 (38.5)
<40, *n* (%)	0
Liver parameters	
γ-GT, U/L	184 (61–364)
ASAT, U/L	89 (44–118)
ALAT, U/L	62 (23–100)
Bilirubin (total), mg/dl	2.7 (1.5–6.5)
Inflammatory markers	
CRP, mg/L	11.94 (7.6–20)
Leucocytes, µl	11.7 (4.8–17.1)

Continuous data are listed as median (IQR).

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; ECLS, extracorporeal life support; IQR, interquartile range; LAS, lung allograft score; LTx, lung transplantation; MRGN, multi-resistant gram-negative bacteria; RA/PA, right atrium/pulmonary artery; SAH, subarachnoid hemorrhage.

The median intensive care unit (ICU) stay at the time of listing was 44 (IQR 22–52) days.

In all patients, irreversible lung damage without a reasonable chance to recover was evident. This was defined by at least two failed weaning attempts from ECMO, a lung compliance consistently <20 ml/mbar without a trend for improvement, and clear radiological evidence of extensive parenchymal destruction in all lobes. The consideration for LTx was discussed by a multidisciplinary team involving intensive care physicians, lung transplant physicians, lung transplantation surgeons, anesthesiologists and physiotherapists. In all patients the neurological status was evaluated and when sedation could not be reduced to determine intact neurology, a CT of the brain was performed. The median lung allocation score (LAS) was 76 (IQR 50–85) (LAS > 50 corresponds to a "high LAS" status). The lung allograft score (LAS) which was used for all patients refers to the Eurotransplant LAS score.[22] At the time of listing the mean age was 29.2 (±3.6) years, the youngest patient at the time of lung transplantation was 2 years and the oldest 45 years old. Catecholamine support had been needed in 5 (38.5%) patients during their ICU stay, but at the time of listing none of the patients required doses >0.1 µg/kg/min. Kidney parameters (creatinine and Bun) were 0.54 mg/dl (IQR 0.32–0.88), BUN 8.6 mg/dl (IQR 6.2–13.9). All patients had an eGFR > 40ml/min. γ-GT (U/L), ASAT (U/L), ALAT (U/L), and total bilirubin (U/L) at the time of listing were 184 (IQR 61–364), 89 (IQR 44–118), 62 (IQR 23–100), and 2.7 (IQR 1.5–6.5), respectively. CRP was slightly elevated with 11.9 mg/L (IQR 7.6–20) but leucocytes were normal with 11.7×10^9/L (IQR 4.8–17.1). Recipient characteristics are detailed in Table 1. The median time between referral to ICU and LTx listing was 42.5 days (IQR 17.5–50.5). Standard screenings such as echocardiography, HLA screening, virology, abdominal ultrasound or abdominal CT scan and brain imaging for transplantation evaluation were performed. Coloscopy/gastroscopy or coronary angiogram were not included in the pre-LTx evaluation due to the young age of the recipients and an unremarkable medical history.

In a subgroup analysis of patients treated at the Medical University of Vienna, the largest contributing center to this study, we retrospectively analyzed all patients with ARDS who were admitted to the intensive care unit between March 2013 and March 2020.

In total, we could identify 1161 patients with ARDS. 22/1161 patients (1.9%) were referred to the lung transplantation team to consider lung transplantation as a potential therapeutic option. 12/22 patients (54.5%) were female and the mean age of those 22 patients was 42.6 (±4.2) years. At the time patients were first seen by the LTx team, 14/22 patients were bridged on ECMO and 18/22 (81.8%) on mechanical ventilation.

In total, five patients were considered as potential candidates based on the selection criteria provided above for LTx. One patient died during the waiting time and the other four were listed and successfully transplanted (see Figure 3: cases 7, 11, 12, and 13). The remaining 17/22 patients were not eligible for several reasons (older >65 years and comorbidities) for lung transplantation: 7 (31.8%) patients died during their intensive care unit stay due to multi-organ failure. In total 10 of the 22 (45.5%) referred patients recovered and discharged from the intensive care unit (Table 2).

TABLE 2 Characteristics of ARDS patients with no lung transplantation

Number of patients	10
Cause of ARDS, *n* (%)	
Brochiectasia, acute caesarean section	1 (10)
Pneumonia bilateral	4 (0)
Aspiration (intoxication)	1 (10)
AECOPD	2 (20)
AE-IPF	1 (10)
Asthma exacerbation	1 (10)
Age, years	45.5 (±5.3)
Gender, female (%)	5 (50)
Days from transplant referral	3 (1–16.8)
CT scan changes	
Dense consolidation bilateral widespread ground-glass attenuation, mainly lower lobes	6 (60)
Dense consolidation unilateral	4 (40)
At time of ICU admission	
Compliance, ml/cm H_2O	19.3 (9.3–25.7)
P/F ratio, mm Hg	148 (120.3–183.8)
pCO_2, mm Hg	64.9 (49.1–88.5)
ECLS support, *n* (%)	6 (60)
ECLS support, days	8.5 (0–19.3)
ECLS cannulation type	
Veno-venous peripheral	6 (60)
MV, *n* (%)	8 (80)
MV, days	19 (2.3–26.8)
ICU stay, days	22.5 (13.5–33)
Hospital stay, days	27 (19.5–41.5)
Follow up, days	1059 (527.3–1790)
Median survial time, days	969

Continuous data are listed as median (IQR).

Abbreviations: ARDS, acute respiratory distress syndrome; AECOPD, exacerbation of chronic obstructive pulmonary disease; AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; CT, computer tomography; ECLS, extracorporeal life support; ICU, intensive care unit; IQR, interquartile range; MV, mechanical ventilation; P/F ratio, P/F ratio, mm Hg, partial pressure of oxygen, measured at 100 FiO_2; pCO_2, partial pressure of carbon dioxide.

3.2 | Donor characteristics

All recipients received their lungs from a donation after brain death (DBD) donor. The mean donor age was 40.8 (± 5.4) years and 46.2% (*n* = 6) of donors were female. Median P/F ratio before retrieval was 460.5 (IQR 381.3–547.7) mm Hg with a median length of mechanical ventilation of 75.5 (IQR 48–198) h. The most common cause of death was subarachnoid hemorrhage (SAH), followed by trauma, intracerebral bleeding, and anoxic brain damage. Details of donor characteristics are outlined in Table 3.

TABLE 3 Donor characteristics

Donors	*n* = 13
Age, years	40.8 (±5.4)
Gender, female (%)	6 (46.2)
BMI	24.3 (±1.7)
P/F ratio, mm Hg	460.5 (381.3–547.7)
Type of donor, DBD (%)	13 (100)
Time of ventilation, h	75.5 (48–198)
Smoker, *n* (%)	6 (46.2)
TLC, L	5.4 (5.1–6.6)
Oto score	4 (1–5)
Cause of death, *n* (%)	
SAH	4 (30.8)
ICB	2 (15.4)
Trauma capitis	2 (15.4)
Anoxic brain damage	2 (15.4)
Other	3 (23.1)

Continuous data are listed as median (IQR).

Abbreviations: BMI, body mass index; DBD, donor after brain-stem death; ICB, intracerebral bleeding; IQR, interquartile range; P/F ratio, P/F ratio; mm Hg, partial pressure of oxygen, measured at 100 FiO_2; SAH, subarachnoid hemorrhage; TLC, total lung capacity.

3.3 | Transplantation

At the time of LTx, the median time on mechanical ventilation and ECMO support were 46 days (IQR 39–71) and 39 days (IQR 24–54), respectively.

The most common surgical approach was a clamshell incision (*n* = 10; 76.9%). In three patients (23.1%) two separate anterior thoracotomies were performed. Bilateral lung transplantation was performed in 12 (92.3%) patients, one patient underwent a single right LTx. Due to size mismatch 4 (30.7%) grafts had to be downsized. In 2 (15.4%) patients, the lingula and middle lobe were resected and 2 (15.4%) patients received a trilobar lung transplantation.

Naturally, all lung transplantations were performed with mechanical circulatory support. In 6 (46.2%) patients a central VA ECMO was used and in 4 (30.8%) patients the preexisting VV ECMO was continued. In one patient, a peripheral femoral-femoral VA ECMO was inserted. Central cardiopulmonary bypass (CPB) was used in two patients (15.4%). LTx was complicated in most cases due to severe adhesions and an increased tendency to bleed. A median of 6.5 (IQR 2.3–12.5) packed red blood cell (pRBC) concentrates and 11 (IQR 4–18) units of fresh frozen plasma (FFP) were required intra-operatively.

3.4 | Postoperative Outcome

Five (38.5%) patients received induction therapy (basiliximab *n* = 3; antithymocyte globulin [ATG] *n* = 1; alemtuzumab *n* = 1) and maintenance immunosuppression was based on a standard triple-regimen

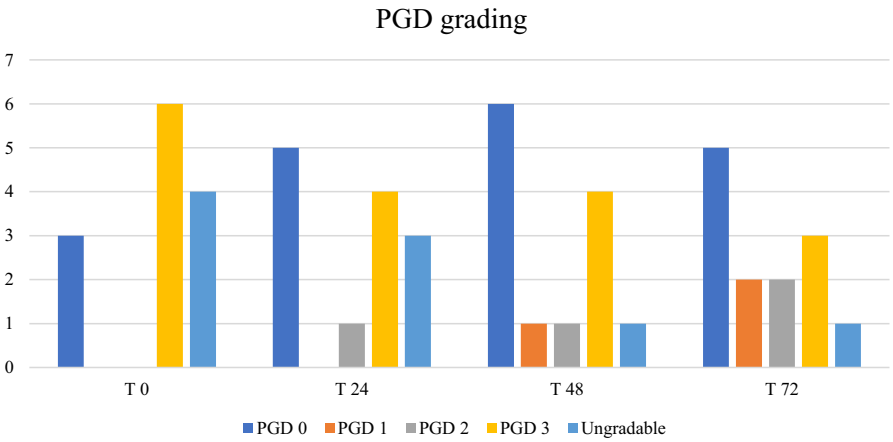

FIGURE 1 PGD grading: PGD grading according to the ISHLT guidelines[21] within the first 72 h postoperative for all 13 patients. Four out of 13 (30.8%) patients with a prolonged prophylactic ECMO support were graded as PGD "ungradable" at T 24 h. PGD grade 3 was seen in 6 (46.2%) patients. Graft function improved significantly thereafter and only three patients remained in PGD 3 at T72 h

TABLE 4 Perioperative complications

Perioperative complications	*n* = 13
Postoperative hemorrhage, *n* (%)	4 (30.8)
Thrombosis jugular vein, *n* (%)	2 (15.4)
Sternal dehiscence, *n* (%)	1 (7.7)
Pneumonia, *n* (%)	1 (7.7)
Groin infection, *n* (%)	1 (7.7)

in all recipients. PGD grading was performed according to the most recent ISHLT guideline.[21] Seven (53.8%) patients required a prolongation of peripheral ECMO support into the early postoperative period, 4 (30.8%) patients were scored with PGD ungradable due to the use of ECMO for non-hypoxic indications without pulmonary edema on chest X-ray imaging.

The used cannulation type was uniformly a femoral-femoral VA-ECMO and the median duration of postoperative ECMO was 2 (IQR 2–7) days. Figure 1 depicts PGD scores within the first 72 h postoperatively based on the most recent ISHLT classification.[21] At T24 h, PGD grade 3 was documented in 6 (46.2%) patients. 4/13 (30.8%) patients with a prolonged ECMO support were graded as PGD "ungradable". At the time points T48 and T72 h, graft function improved significantly and only three patients remained in PGD 3 at T72 h.

Perioperative complications were documented in 9 (69.2%) patients and are outlined in Table 4. Four patients (30.8%) had to be brought back to the operating room for bleeding. An ECMO-related thrombosis of the jugular vein was recorded in 2 (15.4%) patients. All patients were scanned with ultrasound after decannulation. All ECMO cannulas are heparin coated.

Cannulation sites were routinely scanned by Doppler ultrasound after decannulation.

The median length of mechanical ventilation was 33 days (IQR 17–52.5), median time on ICU was 39 (IQR 19.5–58.5) days, and the median length of hospital stay was 54 (IQR 43.5–127) days.

Two patients required transient renal replacement therapy during their postoperative ICU stay (patient #4 for 8 days, patient #12 for 19 days). Both patients fully recovered their kidney function. A third patient (patient #2) experienced a slow posttransplant decline in renal function due to calcineurin toxicity. In this patient, hemodialysis had to be started 825 days after LTx.

Within the first 30 days one patient died (7.7%) from sepsis and consecutive multi-organ failure (MOF). All other patients could be discharged in good clinical condition.

Patient number 7 had pre-formed donor-specific anti-HLA antibodies (class II). Patient number 7 was in total 29 days on veno-venous ECMO and 3 packed red blood cell (pRBC) concentrates were substituted before LTx. The patient received pre- and posttransplant immunadsorption in addition to 7 cycles of extracorporeal photophoresis after the transplantation. During lung transplantation the patient received 7 packed red blood cell concentrates (pRBC) and 18 units of fresh frozen plasma (FFP). At the time of hospital discharge, panel reactivity (PRA) was still 63% (IgG). Despite all efforts she subsequently deteriorated with her graft function and passed away on POD164 due to AMR.

3.5 | Follow-up

The median follow-up time was 536 (IQR 142–1524) days. 1 and 5-year survival rates were calculated as 71.6% and 54.2%, respectively (Figure 2). The median survival time was 590 days (Figure 2). A detailed list of outcome parameters, survival, and follow-up for each patient is provided in Figure 3.

4 | DISCUSSION

To the best of our knowledge, this is the first large case series describing peri- and postoperative outcomes of LTx for ARDS in the ET region. In total, we could identify 13 transplantations for ARDS in three high-volume centers over a time period of 22 years. Only one patient was lost in the early postoperative period, resulting in a 30-day mortality rate of 7.7%. This procedure-related mortality is comparable to non-ARDS patients bridged to transplantation with ECLS.[23] Although early outcome was encouraging, 5/13 patients died within 5 years after transplantation. However, when looking into the respective causes of death

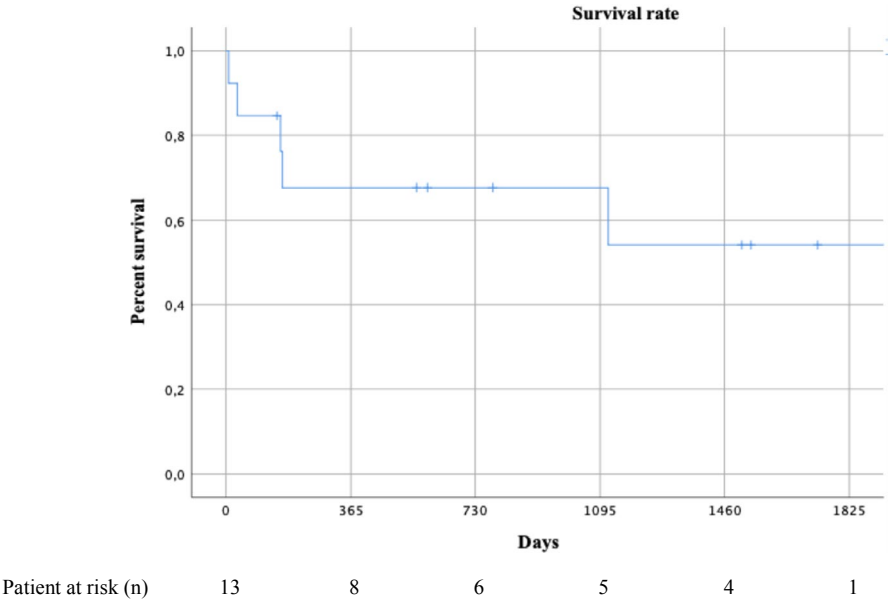

FIGURE 2 Survival curve 1998–2020: Kaplan–Meier survival curve of all 13 ARDS patients who received a lung transplantation demonstrates 1-year and 5-year survival rates of 71.6% and 54.2%, respectively [Color figure can be viewed at wileyonlinelibrary.com]

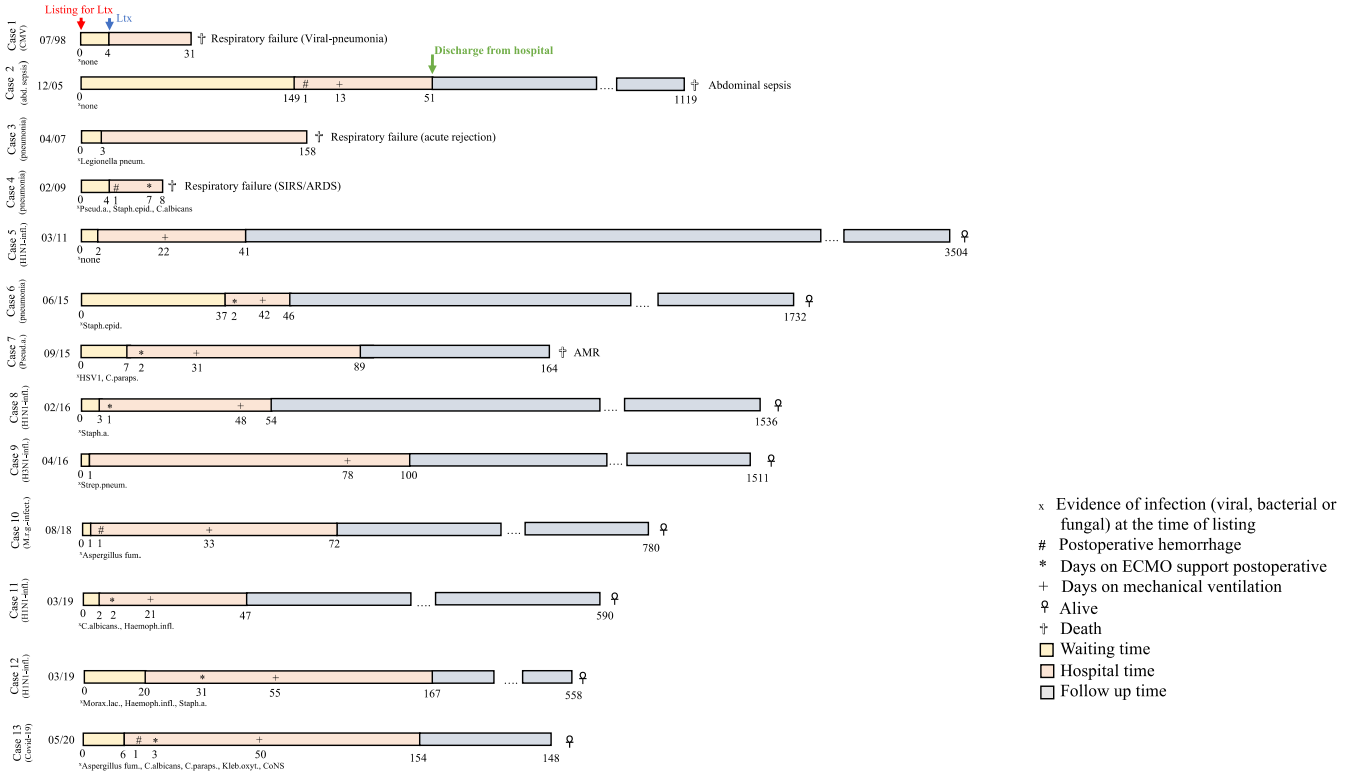

FIGURE 3 Schematic diagram of all 13 patients. All 13 ARDS patients are shown chronically, starting with the time of listing for LTx. Postoperative events such as postoperative bleeding, duration of prolonged ECMO and mechanical ventilation are demonstrated as time points (postoperative days) after LTx. Follow-up time is defined as the time of discharge from hospital to the last follow-up visit. Aspergillus fum., *Aspergillus fumigatus*; C.albicans, *Candida albicans*; C.paraps., *Candida parapsilosis*; CoNs, Coagulase-negative staphylococci; Haemoph. infl., *Haemophilus influenzae*; HSV1, herpes simplex virus; Legionella pneum., Kleb.oxyt., *Klebsiella oxytoca*; *Legionella pneumophila*; Morax.lac., *Moraxella lacunata*; m.r.g.-infect, multi-resistant gram-negative infection; Pseud.a., *Pseudomonas aeruginosa*; Staph.a., *Staphylococcus aureus*; Staph. epid., *Staphylococcus epidermidis*; Strep.pneum., *Streptococcus pneumoniae*

in detail, respiratory failure due to infection was the reason for death in three patients, abdominal sepsis leading to multi-organ failure in one patient and antibody-mediated rejection (AMR) in one patient. We therefore believe that this impaired long-term survival is not related to the indication or the perioperative challenges associated with ARDS.

Thrombosis of the jugular vein is very common when used for ECMO cannulation.[24] The rate of jugular vein thrombosis was 15%

in our study. In the two patients with thrombosis, an occlusion of the external jugular vein was observed. Nine patients (69.2%) were bridged with a femoral-jugular ECMO and one patient with a jugular double-lumen cannula. All patients were assessed with ultrasound after decannulation. Notable, all ECMO cannulas are heparin-coated. In a single-center study performed by anaesthesits from the Medical University of Vienna, which was the biggest contributing center to this ARDS study, it was demonstrated that subcutaneous low molecular weight heparin (bid) is associated with a lower rate of thromboembolic events in patients with perioperative ECMO compared to unfractioned intravenous heparin.[25] Maybe this different anticoagulation regime was a contributing factor to the low rates of jugular vein thrombosis.

In this case series, early mortality was almost exclusively seen in the earliest cases, providing evidence for a learning curve (era-effect). Within the last decade experience in ECLS bridging, surgical techniques as well as intra- and perioperative handling have improved significantly. Consequently, all ARDS cases transplanted after 2016 are still alive. Currently, a pan-European study is recruiting centers, which are willing to contribute patients, in order to confirm early and late mortality of LTx for ARDS in a larger cohort of patients.

One of the main obstacles in LTx for ARDS remains the selection of potential candidates. Considerations include age (<65 years), the function of other organs, sufficient time passed to allow the lungs to recover (>2 weeks) and radiological evidence of irreversible lung damage. In addition, the standard selection criteria for transplantation as previously defined by the ISHLT should be respected (ie adequate body-mass index, absence of notable comorbidities, no recent history of malignancy, etc).[14,26]

Recently, an Eurotransplant (ET) LAS Review Board expert consensus was reached for exceptional lung allograft score (eLAS) approval for ARDS patients on MV/ECMO, which include most of the above-mentioned aspects: (i) lack of clinical improvement despite optimized therapy for at least 2 weeks, (ii) absence of significant ECMO-related complications such as major bleeding/emboli, (iii) preserved cardiac and liver function (a transient kidney failure is not considered a contraindication for LTx), (iv) absence of significant extrapulmonary disease, (v) absence of neurological damage, and (vi) absence of untreated or uncontrolled infection. (LAS Reviewer Board Meeting 09/07/2020, P-ThAC04.2020, currently under review by ET Thoracic Advisory Committee [EThAC] for implementation as ET business rules).

ARDS patients of this study were granted a median LAS of 76, indicating the high acuity of this population. The Eurotransplant (ET) lung allograft score (LAS) was implemented for allocating lung allografts and facilitate cross-border exchange of organs for high-urgent recipients. The score allows to estimate each candidate's medical status prior to transplantation and the probability of success after transplantation. Parameters for assessing the score are: age, underlying disease, height and weight, diabetes, supplemental oxygen requirement/need for assisted ventilation, six-minute walk distance, pulmonary artery pressure, mean pulmonary capillary wedge pressure, forced vital capacity, serum creatinine, functional status, current, lowest and highest pCO_2. Scores ≥50 are considered as "high LAS".[22] The median LAS for the overall waitlist population in the Eurotransplant region is 32.[22]

The patients of our case series were all younger than 40 years. Despite this, the chronological age of an ARDS patient should not be a selection criterion; however, the functional reserve and pre-existing frailty are important factors, which determine the success of lung transplantation. Currently, there is no objective score or reliable tool to quantify the frailty in LTx candidates and the rehabilitation potential. Therefore, the likelihood of a full recovery is individually assessed by a multidisciplinary team including lung transplantation surgeons, pneumologists, intensive care unit physicians and physiotherapists. Recently, objective measures of frailty, which could be also used in sedated and ventilated patients have been proposed. These include core body muscle area and cross-sectional area of mediastinal fat.[27–29]

Within the last decade, the use of ECMO in ARDS has increased significantly.[18,30] This technology allows the lungs to recover by reducing the driving pressure on the ventilator. On the other hand, it can also be used to bridge patients to lung transplantation.[3,6–8,31–35] In such a setting it is important to wean the patients off any sedation and start intensive physiotherapy as soon as possible. In some cases, patients can even be mobilized. This "awake ECMO"-concept is opposed to the traditional view that neuromuscular blockade should be part of the therapy for severe ARDS. Already 2–3 days after initiation of mechanical ventilation, the diaphragm can lose up to 50% of its fibers,[36] which can pose substantial hindrance to posttransplant recovery.

It is currently a matter of debate how much time an ARDS lung should be given to recover. Anecdotal reports of patients treated by ECMO > 100 days before their lungs started to recover can be found in the literature. However, such long ECMO runs are associated with a high risk of bleeding, thromboembolic complications, neurological complications, infections, and vascular complications.[37] Therefore, the factor time is essential when discussing LTx for ARDS and there is a window of opportunity for potential candidates, which must not be missed.

We find the decision which ARDS patients should be transplanted and when to transplant extremely difficult as the likelihood of lung recovery is sometimes hard to predict. We have learned in post-COVID patients that a considerable number of ARDS patients recover their lung function after several weeks or even months of ECMO. In these patients, we found that repeated CT scans and the trend in lung compliance useful parameters to distinguish between patients who will recover and patients who will not recover. In CT scans the amount of ground glass, which is reversible, opposed by areas of fibrosis has evolved as an important selection criterion. However, additional factors such as bacterial superinfections, parenchymal necrosis, bronchopleural fistula and empyema have to be taken into consideration when patients are referred to the LTx team. In this series, it was evident for all transplanted cases, that the likelihood of lung recovery was minimal.

In our series, three patients developed acute kidney failure. Notably, at the time of listing all patients had fully recovered kidney

function and eGFR was >40 ml/min in all cases. During the early phase of ECMO oliguria is commonly observed, but often recovers after 48 h.[38,39]

This study shows that LTx for ARDS is complex and the perioperative management is demanding. Similar to non-ARDS patients with ECMO support awaiting LTx, lung implantation is challenging due to adhesions and an impaired coagulation after prolonged ECMO bridging. This results in a higher risk for ischemic-reperfusion injury and primary graft dysfunction.[12] Therefore, some LTx centers have started to liberally prolong a VA ECMO into the early postoperative course. This facilitates a lung protective ventilation strategy and allows a prolonged controlled graft reperfusion. The beneficial effects of this concept have recently been highlighted.[33,40]

In the herein reported patient cohort, a relatively high rate of postoperative complications was recorded. Four (30.7%) patients had to be brought back to the operation room for hemothorax. Bleeding related to severe adhesions has been observed as a common problem in patients transplanted post-COVID ARDS.[12,41] In the herein described series of non-COVID ARDS patients, we observed similar rates of severe adhesions and bleeding during the transplantation and postoperatively. Lung transplantation for ARDS is challenging due to fragile tissue quality, chronic inflammatory changes and necrotizing lung tissue. All these factors make it difficult to control the lung hilum. Once, the hilum is clamped and the destroyed lung is removed, bleeding from chest wall can be addressed.

The majority of patients were severely deconditioned and a long ICU stay and prolonged rehabilitation was expected. The often tedious perioperative course of ARDS recipients requires substantial experience with complex transplantations and ECMO handling. Thus, this treatment should only be offered by high-volume lung transplant centers with an established expertise in LTx of ECLS-bridged patients.

Thrombosis of the jugular vein is a common finding after prolonged VV ECMO.[24] The rate of jugular vein thrombosis was surprisingly low in our study (15%). All patients were assessed with Doppler ultrasound after decannulation. Notably, all ECMO cannulas were heparin coated. In a single-center study performed by anesthesits from the Medical University of Vienna, which was the biggest contributing center to this ARDS study, it was demonstrated that subcutaneous low molecular weight heparin (bid) is associated with a lower rate of thromboembolic events in patients with perioperative ECMO compared to unfractioned intravenous heparin.[25] Maybe this different anticoagulation regime was a contributing factor to the low rates of jugular vein thrombosis.

Another important aspect which needs to be discussed are ethical implications related to LTx for ARDS. Although early outcome was excellent in our patient cohort, long-term survival was lower than the benchmark of LTx for standard indications. Consequently, the question arises if it is ethically justified to allocate organs to ARDS patients. The lack of alternative therapies and the often young age of the patients are strong ethical arguments in favor of this concept. Weighing the outcome of different indications to decide if a patient can be listed is dangerous and will result in only accepting "easy" patients with the best perioperative outcome. However, regional organ availability and wait list mortality have to be included in the decision if ARDS patients can be accepted for LTx. The wait list mortality of Belgium, The Netherlands and Austria currently ranges between 3% and 8%—a consequence of steadily expanding the donor pool in the last years. In our opinion, with such a low wait list mortality, eligible ARDS patients should not be deprived of LTx as the only life-saving therapy.

Our study has several limitations. First, the number of analyzed patients is low. Although data granularity was high, comparative statistical tests or subgroup analysis could not be performed. Currently, a pan-European study on ARDS patients treated by LTx is recruiting patients and we hope that this will result in a larger cohort allowing these analyses. Second, the selection criteria which were used by the three LTx centers of this study are purely experience-based and represent personal views. Future studies are needed to validate these selection criteria. Third, patients referred for but eventually not considered for LTx were not analyzed in detail. These numbers would be needed to gain better insight in the proportion of severe ARDS patients amendable for LTx. Fourth, this is a retrospective analysis with the possibility of miscoded data and missing parameters. Last, the study covers a long time period. As therapies have significantly improved over the years, there is certainly an era effect with improved outcomes in more recent patients.

In conclusion, ARDS for lung transplantation is challenging but it can be considered for a selected group of patients with acute lung failure. Further multi-center series are needed to confirm the herein presented results.

ACKNOWLEDGMENTS

RV is a senior clinical research fellow of the FWO-Flanders. DVR is supported by the Broere Charitable Foundation. This research did not receive any other specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

AUTHOR CONTRIBUTIONS

A.E.F., T.G., D.K., S.S., and F.K. performed the research work and data collection. A.E.F. performed the statistical analysis. K.H., E.V., and R.V. contributed to the conception and design of the study and all authors did the final revision of the article. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Anna E. Frick https://orcid.org/0000-0003-2959-2137
Robin Vos https://orcid.org/0000-0002-3468-9251
Stefan Schwarz https://orcid.org/0000-0002-3570-0766
Dirk E. Van Raemdonck https://orcid.org/0000-0003-1261-0992
Konrad Hoetzenecker https://orcid.org/0000-0001-6775-7460

REFERENCES

1. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994;149(3):818-824.
2. Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. *Nat Rev Dis Primers*. 2019;5:18.
3. Combes A, Hajage D, Capellier G, et al. Extracorporeal Membrane Oxygenation for severe acute respiratory distress syndrome. *N Engl J Med*. 2018;378:1965-1975.
4. Brodie D, Bacchetta M. Extracorporeal Membrane Oxygenation for ARDS in adults. *N Engl J Med*. 2011;365:1905-1914.
5. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1334-1349.
6. Iacono A, Groves S, Garcia J, Griffith B. Lung transplantation following 107 days of extracorporeal membrane oxygenation. *Eur J Cardiothorac Surg*. 2010;37:969-971.
7. Salam S, Kotloff R, Garcha P, et al. Lung transplantation after 125 days on ECMO for severe refractory hypoxemia with no prior lung disease. *ASAIO J*. 2017;63:e66-e68.
8. Licker M, Schweizer A, Hohn L, Morel DR, Spiliopoulos A. Single lung transplantation for adult respiratory distress syndrome after paraquat poisoning. *Thorax*. 1998;53:620-621.
9. Demertzis S, Haverich A. Post-traumatic ARDS–a potential indication for lung transplantation? *Unfallchirurg*. 1993;96:615-617.
10. Brichon PY, Barnoud D, Pison C, Perez I, Guignier M. Double lung transplantation for adult respiratory distress syndrome after recombinant interleukin 2. *Chest*. 1993;104:609-610.
11. Jurmann MJ, Schaefers HJ, Demertzis S, Haverich A, Wahlers T, Borst HG. Emergency lung transplantation after extracorporeal membrane oxygenation. *ASAIO J*. 1993;39:M448-M452.
12. Lang C, Jaksch P, Hoda MA, et al. Lung transplantation for COVID-19-associated acute respiratory distress syndrome in a PCR-positive patient. Lancet. *Respir Med*. 2020;8(10):1057-1060.
13. Jackson A, Cropper J, Pye R, Junius F, Malouf M, Glanville A. Use of Extracorporeal Membrane Oxygenation as a bridge to primary lung transplant: 3 consecutive, successful cases and a review of the literature. *J Heart Lung Transplant*. 2008;27:348-352.
14. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014–an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2015;34:1-15.
15. Pigula FA, Griffith BP, Zenati MA, Dauber JH, Yousem SA, Keenan RJ. Lung transplantation for respiratory failure resulting from systemic disease. *Ann Thorac Surg*. 1997;64:1630-1634.
16. The Toronto Lung Transplant Group. Sequential bilateral lung transplantation for paraquat poisoning. A case report. *J Thorac Cardiovasc Surg*. 1985;89:734-742.
17. Barrio J, Sánchez C, Vicente R, et al. Successful sequential double-lung transplantation for adult respiratory distress syndrome after long-term mechanical ventilation. *Eur J Anaesthesiol*. 2004;21:326-327.
18. Davies A, Jones D, Bailey M, et al. Extracorporeal Membrane Oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA*. 2009;302:1888-1895.
19. Navarro R. Lung transplantation in adult respiratory distress syndrome. *J Heart Lung Transplant*. 1993;12:880.
20. Chang Y, Lee SO, Shim TS, et al. Lung transplantation as a therapeutic option in acute respiratory distress syndrome. *Transplantation*. 2018;102:829-837.
21. Snell GI, Yusen RD, Weill D, et al. Report of the ISHLT Working Group on primary lung graft dysfunction, part I: definition and grading-A 2016 consensus group statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2017;36:1097-1103.
22. Smits JM, Nossent G, Evrard P, et al. Lung allocation score: the Eurotransplant model versus the revised US model - a cross-sectional study. *Transpl Int*. 2018;31:930-937.
23. Benazzo A, Schwarz S, Frommlet F, et al. Twenty-year experience with extracorporeal life support as bridge to lung transplantation. *J Thorac Cardiovasc Surg*. 2019;157:2515–2525.e10.
24. Menaker J, Tabatabai A, Rector R, et al. Incidence of cannula-associated deep vein thrombosis after veno-venous extracorporeal membrane oxygenation. *ASAIO J*. 2017;63:588-591.
25. Gratz J, Pausch A, Schaden E, et al. Low molecular weight heparin versus unfractioned heparin for anticoagulation during perioperative extracorporeal membrane oxygenation: a single center experience in 102 lung transplant patients. *Artif Organs*. 2020;44:638-646.
26. Cypel M, Keshavjee S. When to consider lung transplantation for COVID-19. *Lancet Respir Med*. 2020;8(10):944-946.
27. Weig T, Milger K, Langhans B, et al. Core muscle size predicts postoperative outcome in lung transplant candidates. *Ann Thorac Surg*. 2016;101:1318-1325.
28. Pienta MJ, Zhang P, Derstine BA, et al. Analytic morphomics predict outcomes after lung transplantation. *Ann Thorac Surg*. 2018;105:399-405.
29. González FJ, Alvarez A, Cantador B, et al. Relationship among radiological measurements of anterior mediastinal fat and outcomes of lung transplantation in fibrotic patients. *Arch Bronconeumol*. 2020;56:710-717.
30. Mols G, Loop T, Geiger K, Farthmann E, Benzing A. Extracorporeal membrane oxygenation: a ten-year experience. *Am J Surg*. 2000;180:144-154.
31. Manert W, Haller M, Briegel J, et al. Venovenous Extracorporeal Membrane Oxygenation (ECMO) with a heparin-lock bypass system. An effective addition in the treatment of acute respiratory failure (ARDS). *Anaesthesist*. 1996;45:437-448.
32. Bermudez CA, Rocha RV, Sappington PL, Toyoda Y, Murray HN, Boujoukos AJ. Initial experience with single cannulation for venovenous extracorporeal oxygenation in adults. *Ann Thorac Surg*. 2010;90:991-995.
33. Hoetzenecker K, Donahoe L, Yeung JC, et al. Extracorporeal life support as a bridge to lung transplantation-experience of a high-volume transplant center. *J Thorac Cardiovasc Surg*. 2018;155:1316-1328.e1.
34. Turner DA, Rehder KJ, Bonadonna D, et al. Ambulatory ECMO as a bridge to lung transplant in a previously well pediatric patient with ARDS. *Pediatrics*. 2014;134:e583-e585.
35. Kon ZN, Wehman PB, Gibber M, et al. Venovenous Extracorporeal Membrane Oxygenation as a bridge to lung transplantation: successful transplantation after 155 days of support. *Ann Thorac Surg*. 2015;99:704-707.
36. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med*. 2008;358:1327-1335.
37. Lo Coco V, Lorusso R, Raffa GM, et al. Clinical complications during veno-arterial extracorporeal membrane oxigenation in post-cardiotomy and non post-cardiotomy shock: still the achille's heel. *J Thorac Dis*. 2018;10:6993-7004.
38. Kielstein JT, Heiden AM, Beutel G, et al. Renal function and survival in 200 patients undergoing ECMO therapy. *Nephrol Dial Transplant*. 2013;28:86-90.
39. Makdisi G, Wang IW. Extra Corporeal Membrane Oxygenation (ECMO) review of a lifesaving technology. *J Thorac Dis*. 2015;7:E166-E176.
40. Hoetzenecker K, Schwarz S, Muckenhuber M, et al. Intraoperative extracorporeal membrane oxygenation and the possibility of

postoperative prolongation improve survival in bilateral lung transplantation. *J Thorac Cardiovasc Surg*. 2018;155:2193-2206.e3.
41. Bharat A, Machuca TN, Querrey M, et al. Early outcomes after lung transplantation for severe COVID-19: a series of the first consecutive cases from four countries. *Lancet Respir Med*. 2021;9(5):487-497. S2213-600(21)00077-1.

How to cite this article: Frick AE, Gan CT, Vos R, et al. Lung transplantation for acute respiratory distress syndrome: A multicenter experience. *Am J Transplant*. 2022;22:144–153. https://doi.org/10.1111/ajt.16759