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Lung transplantation for acute respiratory distress syndrome: a retrospective European cohort study

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Shareable abstract (@ERSpublications)
Most ARDS patients are bridged by mechanical support to LTx. 40 patients were identified in 48 European centres. 31 survived until transplantation and 1-year survival was 71% after LTx. The selection process remains ethically challenging. https://bit.ly/3GKwPL3

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Abstract

Background The published experience of lung transplantation in acute respiratory distress syndrome (ARDS) is limited. The aim of this study was to investigate the contemporary results of lung transplantation attempts in ARDS in major European centres.

Methods We conducted a retrospective multicentre cohort study of all patients listed for lung transplantation between 2011 and 2019. We surveyed 68 centres in 22 European countries. All patients admitted to the waitlist for lung transplantation with a diagnosis of "ARDS/pneumonia" were included. Patients without extracorporeal membrane oxygenation (ECMO) or mechanical ventilation were excluded. Patients were followed until 1 October 2020 or death. Multivariable analysis for 1-year survival after listing and lung transplantation was performed.

Results 55 centres (81%) with a total transplant activity of 12 438 lung transplants during the 9-year period gave feedback. 40 patients with a median age of 35 years were identified. Patients were listed for lung transplantation in 18 different centres in 10 countries. 31 patients underwent lung transplantation (0.25% of all indications) and nine patients died on the waitlist. 90% of transplanted patients were on ECMO in combination with mechanical ventilation before lung transplantation. On multivariable analysis, transplantation during 2015–2019 was independently associated with better 1-year survival after lung

transplantation (OR 10.493, 95% CI 1.977–55.705; p=0.006). 16 survivors out of 23 patients with known status (70%) returned to work after lung transplantation.

Conclusions Lung transplantation in highly selected ARDS patients is feasible and outcome has improved in the modern era. The selection process remains ethically and technically challenging.

Introduction

A distinct type of hypoxaemic respiratory failure characterised by acute abnormality of both lungs was described during the 1960s and subsequently termed acute respiratory distress syndrome (ARDS). The Berlin Definition of ARDS was published in 2012, and described disease severity by oxygenation impairment and respiratory mechanics [1]. ARDS had a 35–46% hospital mortality dependent on disease severity in the LUNG-SAFE Study [2]. In a recent analysis of more than 45 000 ARDS patients on venovenous extracorporeal membrane oxygenation (ECMO) in Germany, hospital mortality was 54% [3]. In a multicentre US cohort including 646 ARDS patients, 1-year survival was 59% with 22% dying after initial hospital discharge [4].

Supportive treatment including prolonged mechanical ventilation and ECMO in severe cases is the standard of care. Recovery from the disease and weaning from respiratory support become more unlikely when late fibrotic stages of the disease are evident. In these patients, signs of irreversible lung disease are typically present on high-resolution computed tomography.

The published experience of lung transplantation in ARDS was limited to single-centre case series until 2020 [5–14] and was regarded as controversial for many years because survival was inferior in comparison with patients suffering from chronic lung diseases. Many centres were reluctant to accept these patients because they are challenging to evaluate and are usually unable to give consent.

Coronavirus disease 2019 (COVID-19) is a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since December 2019, COVID-19 has spread worldwide, leading to a pandemic and need for mechanical ventilation in 2–3% of infected cases with high mortality [15]. Increasingly, lung transplantation centres are confronted with lung transplantation requests of patients with severe COVID-19-related respiratory failure on mechanical respiratory support.

The objective of this study was to analyse the European experience of lung transplantation for ARDS before the COVID-19 pandemic to facilitate case discussion of this approach because of similarities.

Methods

A retrospective multicentre cohort study was conducted. A study period between 2011 and 2019 was chosen because 1) in 2011, the Lung Allocation Score (LAS) was introduced in Eurotransplant with unified coding of diseases, 2) recent cases with contemporary management and sufficient follow-up time were included, and 3) a focus was made on the pre-pandemic era. European lung transplant centres were identified *via* the registry of the International Society for Heart and Lung Transplantation and by personal knowledge.

A survey with case definition and 46 variables per identified case was sent out to 68 centres in 22 European countries. All patients admitted to the waitlist for lung transplantation with a diagnosis of "ARDS/pneumonia" were included. Patients with hospital discharge after the initial diagnosis of ARDS/pneumonia, absence of ECMO or mechanical ventilation and patients with pre-existing respiratory diseases (except asthma) were excluded. The study was performed according to the 1975 Declaration of Helsinki and the standards of the 2008 Declaration of Istanbul. The Ethics Committee at the Hannover Medical School (Hannover, Germany), in addition to local ethics committees in centres, approved the study protocol (9416_BO_K_2020). The dataset was anonymised and informed consent was waived according to local policies. No funding was received. A STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist was completed [16].

Date of last patient status was recorded until end of follow-up on 1 October 2020. Performance status on the patient's follow-up visit was rated on the World Health Organization (WHO) scale as previously published (0=fully active to 5=death) [17]. Return to work (including part-time) was recorded on last status. Verbal responsiveness before lung transplantation was defined as being able to follow commands and communicate *via* writing pads as a surrogate to give informed consent. Long-term dialysis after lung transplantation was defined as the use of renal replacement therapy for >90 days. End of mechanical ventilation after lung transplantation was defined as the first day when no machine support was needed

before discharge. Complications of ECMO were recorded *via* chart review, with major bleeding defined by the need for surgery and minor bleeding defined by a bleeding event without the need for surgery.

Lung pathology before transplant was obtained from explant pathology or open lung biopsy if available and classified according to the presence of three predefined criteria: diffuse alveolar damage, acute fibrinoid organising pneumonia and fibrosis (defined by interstitial matrix deposition). Additional findings were recorded.

National transplant activity was extracted from the European Directorate for the Quality of Medicines and Healthcare, and centre activity from Eurotransplant and centre reports.

Statistical analysis was performed with metric variables expressed as median (interquartile range) and categorical variables as absolute number (percentage) of data entries. Univariate analyses were performed using the Mann–Whitney test for continuous variables and the Chi-squared test for categorical variables. Survival analysis was performed using the Kaplan–Meier method and the differences in survival outcomes between groups were compared using the log-rank test. Binary logistic regression analyses were conducted with 1-year post-listing and post-transplant survival as the dependent variable. The level of significance was set at $\leqslant 0.10$ for including variables identified by univariate analysis between groups. Data were analysed as observed without imputation of missing values.

Results

55 centres (81%) gave feedback with a total transplant activity of 12 438 transplants during the 9-year period. 40 patients were identified and listed in 18 different centres for lung transplantation in 10 different countries (Austria n=5, Belgium n=1, Estonia n=1, Finland n=5, France n=2, Germany n=14, Netherlands n=3, Spain n=4, Sweden n=3, UK n=2). 23 patients were listed in the Eurotransplant region and nine within Scandiatransplant. 38 out of 40 patients (95%) were listed in countries using either the LAS or having a national urgency allocation scheme. Six patients with initial discharge after ARDS and later lung transplantation referral with post-ARDS fibrosis (Oslo n=1, Copenhagen n=2, Essen n=1, Nantes n=1, Barcelona n=1) were excluded. ARDS/pneumonia represented 0.25% of all indications in 48 reporting centres and 0.32% of all indications in the 18 centres with at least one case. A flowchart of patients is displayed in figure 1. Increasing incidence during the study period was not observed (figure 2).

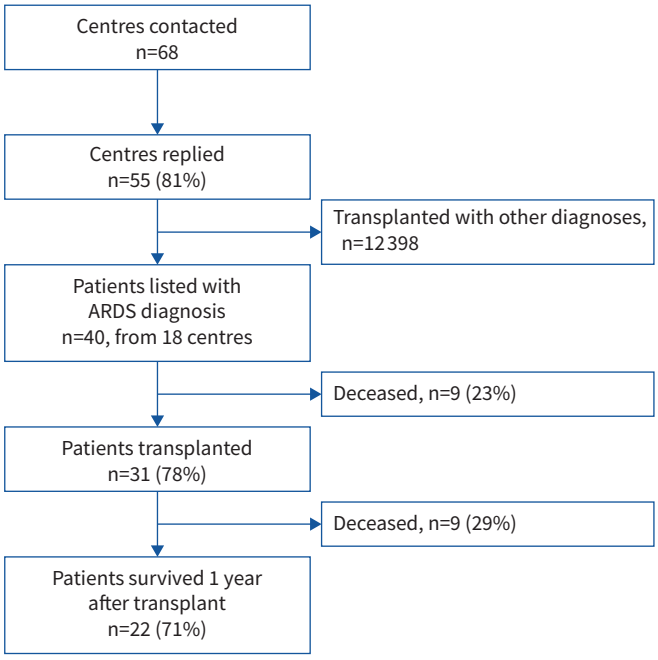

FIGURE 1 Flowchart of patient identification. ARDS: acute respiratory distress syndrome.

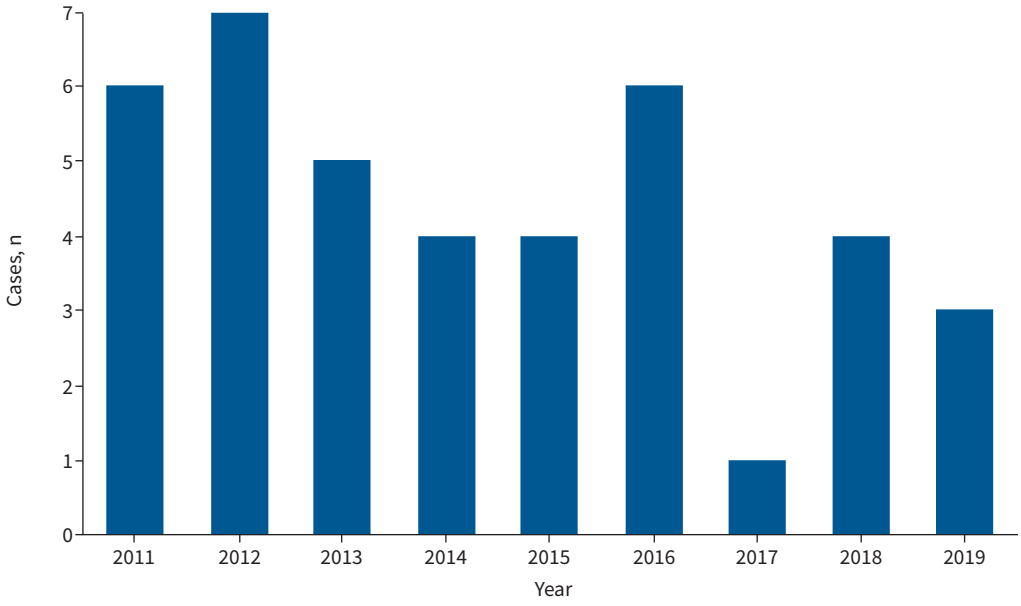

FIGURE 2 Incidence of cases during the study period (n=40).

Patient demographics are displayed in table 1. The median age was 35 years at listing. Three patients (8%) were listed with age <18 years (4, 7 and 16 years). 90% of patients were on ECMO in combination with mechanical ventilation, with a median bridging period before listing of 46 days on mechanical ventilation and 35 days on ECMO. 75% of patients had infectious causes of ARDS, 5% other causes and in 20% aetiology was unknown. The most commonly identified pathogens were influenza virus (n=12), *Streptococcus pneumoniae* (n=3) and cytomegalovirus (n=2).

Data completeness for all variables was 92–100% except for inspiratory oxygen fraction (F_{IO_2}) (68%).

31 (78%) patients were on venovenous ECMO at listing, two (5%) on venoarterial ECMO and three (8%) on venovenous arterial ECMO. A single patient was bridged by an extracorporeal carbon dioxide removal system and another by a pulmonary artery to left atrium ECMO setting. 21 (65%) patients had dual cannulation and eight (25%) had a single, double lumen cannula. Three patients had triple cannulation and in four patients cannulation was unknown. Inflow cannula was mostly positioned in the internal jugular vein and outflow cannula in the femoral vein. In case of a single, double lumen cannula, the right internal jugular vein was preferred.

18 (47%) patients had at least one complication on ECMO. Major bleeding requiring surgical intervention occurred in eight (21%) patients, minor bleeding in six (16%), limb ischaemia/thrombosis in five (13%), clotting of the circuit in three (8%), sepsis in two (5%) and haemolysis in one (3%) during the waiting time.

Outcome

31 patients underwent lung transplantation and nine died while on the waitlist (78% bridging success). Transplant characteristics are displayed in table 2. Donor lungs were allocated by national urgency in 43% and *via* the LAS in 50% after a median waiting time of 14 days. Kaplan–Meier analysis of patient survival after listing comparing patients receiving lung transplantation and those without is shown in figure 3. One-year survival after transplantation was 71%, being not different in seven unilateral lung transplant recipients.

Median (IQR) follow-up after transplantation was 725 (149–1536) days. Three patients required long-term renal replacement therapy after discharge. According to the performance status on last follow-up, eight (26%) patients were fully active, nine (29%) were ambulatory, slightly limited, one (3%) was ambulatory, not active, one (3%) had some support and 12 (39%) were dead. 16 survivors out of 23 patients with known status (70%) returned to work after lung transplantation. Seven patients developed chronic lung

TABLE 1 Patient demographics (n=40)

Female	20 (50)
Age at listing, years	35 (23–46); range 4–62
Any comorbidity	19 (48)
Hypertension	3 (7)
Hypothyroidism	3 (7)
Asthma	2 (5)
Post-pregnancy	2 (5)
Haematopoietic cell transplantation	2 (5)
Renal vasculitis	1 (3)
Rheumatoid arthritis	1 (3)
Irritable bowel syndrome	1 (3)
Sickle cell disease	1 (3)
Thalassaemia	1 (3)
Spherocytosis	1 (3)
Crohn's disease	1 (3)
Cause of ARDS	
Infectious	
Viral	17 (35)
Bacterial	5 (13)
No pathogen identified	8 (20)
Trauma	1 (2)
Nonrespiratory sepsis	1 (2)
Unknown	8 (20)
Ventilation	
MV only	2 (5)
ECMO only	2 (5)
MV plus ECMO	36 (90)
F_{IO_2}	0.61 (0.4–1)
Vasopressor requirement	21 (53)
Verbally unresponsive	18 (45)
Renal replacement therapy before lung transplantation	17 (43)
Rehabilitation/mobilisation pre-transplant	12 (30)
Duration of MV pre-listing, days	46 (22–70)
Duration of ECMO pre-listing, days	35 (20–55)
Follow-up post-listing, days	374 (35–1339)

Data are presented as n (%) or median (interquartile range), unless otherwise stated. ARDS: acute respiratory distress syndrome; MV: mechanical ventilation; ECMO: extracorporeal membrane oxygenation; F_{IO_2}: inspiratory oxygen fraction.

TABLE 2 Transplant patient characteristics (n=31)

Duration of MV pre-transplant, days	65 (36–84)
Duration of ECMO pre-transplant, days	40 (24–72)
Duration on waiting list pre-transplant, days	14 (3–44)
Allocation type	
Elective	2/30 (7)
Emergency	13/30 (43)
LAS	15/30 (50)
Transplant type	
Unilateral	7 (23)
Bilateral	20 (65)
Bilateral lobar	2 (6)
Lung–kidney	1 (3)
Heart–lung	1 (3)
Duration of MV post-transplant, days	21 (4–50); range 0–149

Data are presented as median (interquartile range), n (%) or n/N (%), unless otherwise stated. MV: mechanical ventilation; ECMO: extracorporeal membrane oxygenation; LAS: Lung Allocation Score.

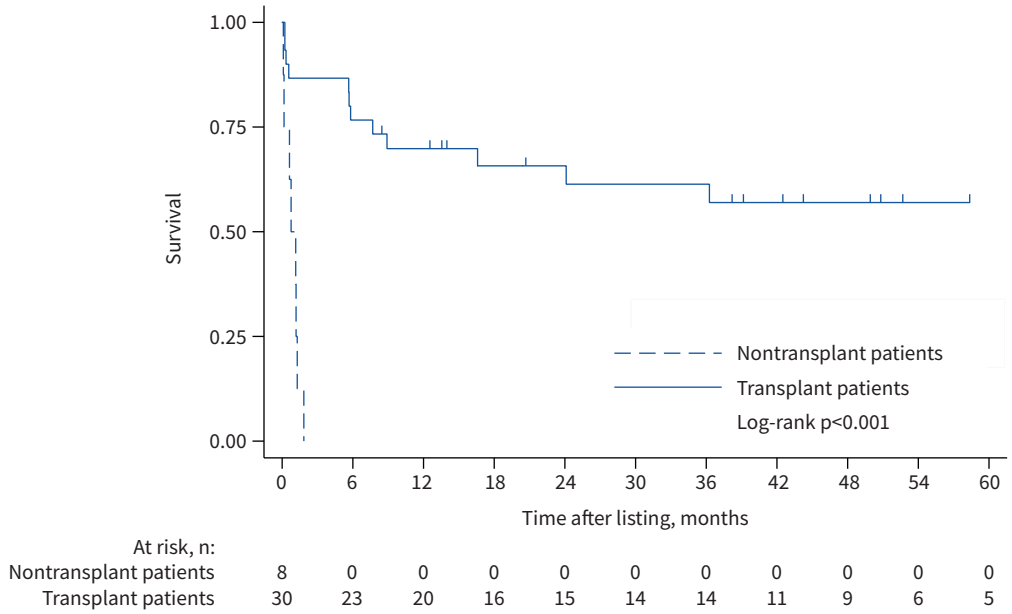

FIGURE 3 Patient survival after listing depending on transplantation status.

allograft dysfunction at a median of 749 days after lung transplantation. All survivors without chronic lung allograft dysfunction (n=14) were fully active (WHO scale 0) or ambulatory with slight limitation (WHO scale 1) at last status.

Lung pathology

Lung pathology was available in 29 patients (in 27 cases obtained by explant pathology and in two cases obtained by open lung biopsy before the listing). In 15 patients (52%) both pulmonary fibrosis (defined by extracellular matrix deposition) and diffuse alveolar damage were found. Four patients (14%) had a pattern of acute fibrinoid organising pneumonia. Additional findings each in a single case (3%) were nonspecific interstitial pneumonia and pleuroparenchymal fibroelastosis. Significant signs of pulmonary hypertension were noted on pathology in three patients.

Predictors of survival

Univariate analysis comparing 1-year survivors with nonsurvivors after listing revealed that none of the following categorised variables had an impact on survival: female gender, age (cut-off 35 years), cause of ARDS (viral *versus* other), type of support, F_{IO_2} (cut-off 0.6), ECMO complication, mobilisation, verbal responsiveness, duration of support, type of transplant, days on waitlist (cut-off 14 days), centre volume (cut-off 50 annual transplants) or number of cases (one or more than one case). In multivariate analysis (with one case excluded due to missing duration of ECMO), lung transplantation was independently associated with survival, while renal replacement therapy before lung transplantation, use of vasopressors, and ECMO complications and duration were not (table 3).

In univariate analysis between 1-year survivors and nonsurvivors after lung transplantation with categorised variables, female gender, age (cut-off 35 years), cause of ARDS (viral *versus* other), type of support, F_{IO_2} (cut-off 0.6), ECMO complication, mobilisation, verbal responsiveness, duration of support, type of transplant, days on waitlist (cut-off 14 days), centre volume (cut-off 50 annual transplants) and number of cases (one or more than one case) were not different. In multivariate analysis, a significantly higher proportion of patients survived >1 year after transplantation in the era 2015–2019, while renal replacement therapy and requirement for vasopressors before lung transplantation were not associated with 1-year lung transplantation survival (table 4). Just one single patient out of nine (11%) who required vasopressors, renal replacement therapy and had an ECMO-related complication survived >1 year after listing.

TABLE 3 Multivariate analysis of predictors of 1-year survival after listing[#]

Covariate	Patients, n	Post-listing survival, n (%)		OR (95% CI)	p-value
		⩽1 year (n=18)	>1 year (n=21)		
Any complications of ECMO (pre-transplant)					
No	21	7 (33)	14 (67)	Reference	Reference
Yes	18	11 (61)	7 (39)	0.199 (0.023–1.716)	0.142
Days of ECMO (pre-listing)					
<30	20	6 (30)	14 (70)	Reference	Reference
⩾30	19	12 (63)	7 (37)	0.140 (0.018–1.109)	0.063
Vasopressor requirement (pre-transplant)					
No	18	5 (28)	13 (72)	Reference	Reference
Yes	21	13 (62)	8 (38)	0.181 (0.021–1.563)	0.120
Renal replacement therapy (pre-transplant)					
No	22	7 (32)	15 (68)	Reference	Reference
Yes	17	11 (65)	6 (35)	0.555 (0.070–4.378)	0.576
Transplant recipient					
No	9	9 (100)		Reference	Reference
Yes	30	9 (30)	21 (70)	52.617 (3.721–744.103)	0.003

ECMO: extracorporeal membrane oxygenation. [#]: one patient excluded due to missing data for ECMO duration.

Discussion

We present a large cohort study of lung transplantation in ARDS collected over a 9-year period in all major lung transplant centres in Europe. According to our collaborative results, ARDS is still a rare indication for lung transplantation in Europe. Most ARDS patients listed for lung transplantation were on invasive ventilation with a combined use of venovenous ECMO before lung transplantation. In this selected cohort of young adults, bridging success was 78% and 1-year survival was 71% (rising to 88% in the most recent period) with acceptable long-term results.

The concept of transplanting lungs for ARDS has been historically considered on a case-by-case basis, but was not a reasonable option for the vast majority of patients. One obstacle for transplantation is that many patients with ARDS have extrapulmonary infections and sometimes multiresistant pathogens which are difficult to treat. These infections pose a risk factor or contraindication for lung transplantation because of intense immunosuppression to prevent organ rejection after the procedure. Other major reasons to decline ARDS patients are surgical complexity, intensive care unit (ICU)-acquired complications, reduced physical condition and reluctance to evaluate patients under sedation [18].

In comparison with the registry data published recently [19], lung transplantation activity for ARDS/pneumonia was slightly different in the USA between 2005 and 2018 (0.15%) and in Europe between 2011 and 2019 (0.25%), probably explained by focusing more on the recent experience in our study. In contrast, the age profile of recipients was similar (median 34 years *versus* 35 years in the USA in comparison with Europe, respectively) as well as the majority of patients being bridged by ECMO.

TABLE 4 Multivariate analysis of predictors of 1-year survival after lung transplantation

Covariate	Patients, n	Post-transplant survival, n (%)		OR (95% CI)	p-value
		⩽1 year (n=9)	>1 year (n=22)		
Era					
2011–2014	15	7 (47)	8 (53)	Reference	Reference
2015–2019	16	2 (12.5)	14 (87.5)	10.493 (1.977–55.705)	0.006
Vasopressor requirement (pre-transplant)					
No	16	2 (12.5)	14 (87.5)	Reference	Reference
Yes	15	7 (47)	8 (53)	0.751 (0.156–3.616)	0.721
Renal replacement therapy (pre-transplant)					
No	19	3 (16)	16 (84)	Reference	Reference
Yes	12	6 (50)	6 (50)	0.486 (0.081–2.905)	0.429

Case reports are usually not helpful to evaluate the outcome of lung transplantation in ARDS patients bridged by mechanical support because of an imminent publication bias [5–14]. Furthermore, short-term outcome is frequently limited to reporting 30-day, hospital or 3-month survival. Because of prolonged recovery after lung transplantation in critical illness, in our view short-term outcome is better reflected by 1-year survival. In a recent multicentre analysis of 12 lung transplantations in COVID-19 patients on ECMO (median age 47 years) the median follow-up was just 80 days, with one patient still in hospital and one death [20].

The proportion of patients transplanted from ECMO has increased in the USA constantly since 2010 to a proportion of 7.3% in 2019 and 7.4% in the Eurotransplant region [21]. Two retrospective US registry analyses of lung transplantation outcome in patients on mechanical support demonstrated a 1-year survival of 69% during the period between 2005 and 2013 (n=184 patients on ECMO, 35% on ECMO only) [22] and 78% between 2005 and 2017 (n=664 patients on ECMO) [23]. Both studies confirm better outcome in the most recent era after transplantation. This was confirmed by our results, and is possibly explained by improved patient selection, management and advances in medical technology. In both US registry publications, the vast majority of extracorporeal life support system-bridged recipients suffered from an underlying chronic respiratory disease such as an interstitial lung disease, chronic obstructive pulmonary disease or cystic fibrosis. The median ages of 47 and 51 years in these studies were higher than in published series on lung transplantation candidates with ARDS. Usually, patients with ARDS/pneumonia are evaluated for lung transplantation on mechanical support, which limits the possibility of invasive tests (*e.g.* coronary angiography, colonoscopy, *etc.*), which are mandatory in candidates aged >50 years in most centres.

In the first of these two analyses, isolated mechanical support by either ECMO or mechanical ventilation had better 1-year survival than patients bridged with a combination of ECMO and mechanical ventilation [22]. These encouraging results of mechanical support must be weighed against the 1-year survival of 85–89% in patients without mechanical support in the modern area [21, 24] and even higher in experienced centres. Because of urgency-driven systems there is an ethical dilemma of driving allocation towards critically ill patients, leading to a disadvantage of competing patients on the waitlist with presumed superior outcome [25, 26]. In our view, this dilemma can only be solved by limiting listing of these patients on a centre level [27].

Although ARDS continues to be a rare indication for lung transplantation, its proportion is rapidly growing. During the COVID-19 pandemic, a further increase in lung transplantation activity for ARDS has been noted in most countries. Prioritisation in the selection process for lung transplantation is inevitable given the donor shortage. In 2018, 1660 patients aged <60 years were treated in Germany with venovenous ECMO for ARDS in contrast to 375 lung transplantation procedures [3].

The largest single-centre series on lung transplantation for ARDS from South Korea reported on 14 patients listed for lung transplantation between 2008 and 2013 with a median age of 38 years. Nine (64%) were transplanted [28]. Similar to our series, 86% were on mechanical ventilation and 78% survived 1 year. A US registry analysis of 2005–2018 recently identified 63 ARDS patients admitted to the waitlist, of whom 39 were transplanted [19]. No recovery occurred after listing in our study in contrast to one out of nine patients in the Korean cohort who survived 1 year and four out of 24 patients not transplanted who improved in the US analysis and who were removed from the waitlist. The 1-year survival of transplanted patients in the US registry was 77%, excluding seven patients who had not yet reached 1 year.

In the US study, 23% of patients were bridged by ECMO only compared with 5% in our study and none in the Korean series [19, 28]. Consequently, more patients (90%) were on mechanical ventilation plus ECMO support in our series compared with the US analysis (54%). Notably, four patients in the US study were neither on mechanical ventilation nor on ECMO, questioning the severity of ARDS in these cases [29]. Taken together with the very high mortality in our patients who did not get a transplant, these numbers highlight the severity of ARDS in our cohort.

Acceptance of ARDS patients for lung transplantation without personal informed consent is controversial. Surrogate decision making is usually applied in ICU patients who have lost the capacity to participate in the decision-making process. Agreement on treatment preference of patients was only 70% even though surrogates were asked to base their treatment decisions on substituted judgement [30]. In our study, almost half of our patients listed were not verbally responsive, suggesting inability to give personal informed consent. Long-term outcomes in survivors after lung transplantation do not indicate a questioning of this approach, although in our view neurological disorders have to be excluded by imaging techniques in such

patients. No psychiatric issues were reported from European centres in recipients who were transplanted based on substitute decision makers.

A key finding of our study is the excellent survival data recorded in the most recent era, with 88% 1-year and 60% 5-year survival. ARDS patients bridged with mechanical support receive high emergency allocation in most countries using national priority systems or the LAS [18, 19, 31–33]. Reporting multi-institutional outcomes of rare indications is essential to pursue this practice. The observed proportion of survivors returning to work (70%) was similar (77%) to a series of 109 ARDS survivors who did not require lung transplantation with a median age of 44 years [34]. Considering that the lung transplantation cohort is usually comprised of the sickest patients, this is another argument for offering this procedure to selected patients.

In general, bilateral rather than unilateral lung transplantation was chosen in most patients because lungs with long-standing ARDS were frequently infected with difficult-to-treat pathogens and demonstrated pulmonary cavities, bilateral pneumothorax, diffuse pulmonary haemorrhage or signs of irreversible lung disease. In addition, some patients had signs of pulmonary hypertension before transplantation, pointing towards the bilateral procedure to avoid severe primary graft dysfunction.

A limitation of our study is still a low number of patients. It is difficult to give recommendations on individual patient selection based on our data. Extrapulmonary organ failure, probably with the exception of acute kidney failure, remains a contraindication in these patients in our experience. Eurotransplant is currently discussing selection criteria for ARDS patients and business rules for allocation.

In conclusion, this cohort study demonstrates the feasibility of lung transplantation in highly selected ARDS patients. In the modern era of lung transplantation and ICU management, results have improved considerably in critically ill candidates with encouraging long-term results in young patients. Because of the severe donor shortage, the outcome of critically ill patients must be balanced against the usually excellent results in elective patients on the waitlist. The selection process is ethically and technically challenging, and the approach should probably be limited to younger patients (<50 years) in the absence of significant additional risk factors. Further studies are warranted to define overarching criteria for lung transplantation in ARDS patients in order to maintain a fair distribution of scarce donor organs.

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Anonymised participant data will be made available after publication upon requests directed to the corresponding author. Proposals will be reviewed and approved by the investigators and collaborators on the basis of scientific merit.

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