ORIGINAL ARTICLE

Outcome of Patients with Interstitial Lung Disease Treated with Extracorporeal Membrane Oxygenation for Acute Respiratory Failure

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Abstract

Rationale: Patients with interstitial lung disease and acute respiratory failure have a poor prognosis especially if mechanical ventilation is required.

Objectives: To investigate the outcome of patients with acute respiratory failure in interstitial lung disease undergoing extracorporeal membrane oxygenation (ECMO) as a bridge to recovery or transplantation.

Methods: This was a retrospective analysis of all patients with interstitial lung disease and acute respiratory failure treated with or without ECMO from March 2012 to August 2015.

Measurements and Main Results: Forty patients with interstitial lung disease referred to our intensive care unit for acute respiratory failure were included in the analysis. Twenty-one were treated with ECMO. Eight patients were transferred by air from other hospitals within a range of 320 km (linear distance) for extended intensive care including the option of lung transplant. In total, 13 patients were evaluated, and eight were finally found to be suitable for lung transplantation from an ECMO bridge. Four patients from external hospitals were *de novo* listed during acute respiratory failure. Six patients underwent lung transplant, and two died on the waiting list after 9 and 63 days on ECMO, respectively. A total of 14 of 15 patients who did not undergo lung transplantation (93.3%) died after 40.3 $\pm$ 27.8 days on ECMO. Five out of six patients (83.3%) receiving a lung transplant could be discharged from hospital.

Conclusions: ECMO is a lifesaving option for patients with interstitial lung disease and acute respiratory failure provided they are candidates for lung transplantation. ECMO is not able to reverse the poor prognosis in patients that do not qualify for lung transplantation.

Keywords: extracorporeal membrane oxygenation; interstitial lung disease; acute respiratory failure; lung transplant

The treatment of patients with interstitial lung disease (ILD) and acute respiratory failure (ARF) is challenging. Currently, the only definitive therapy in pharmacologically refractory ILD is lung transplantation. This is mainly reserved for stable patients that are already on a transplant list. For patients not yet listed, prognosis following intensive care unit (ICU) admission is usually very poor. Most patients who develop ARF based on ILD are unlikely to benefit from extended intensive care treatment (1–5). High-flow oxygen through nasal cannula (hereafter high-flow oxygen) and noninvasive ventilation (NIV) are potential options to avoid intubation in cases of mild ARF (6). In cases of moderate and severe ARF, NIV failure is common (1, 4, 6). Mechanical ventilation is a major problem in patients with ILD who would normally require intubation (1–5). Marked gas exchange impairment and reduced pulmonary compliance lead to high peak and plateau pressures accompanied by a high $F_{I_{O_2}}$. The

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At a Glance Commentary

Scientific Knowledge on the Subject: The management of acute respiratory failure (ARF) in interstitial lung disease (ILD) is difficult. Intubation has been shown to be associated with a mortality rate of up to 90%. In current clinical practice, patients with ARF and ILD are generally not intubated and are given palliative care. Extracorporeal membrane oxygenation (ECMO) is viewed critically because the technology might not allow for the recovery of cardiopulmonary function.

What This Study Adds to the Field: ECMO is a lifesaving option for patients with ILD and ARF provided they are suitable candidates for lung transplantation. In these cases, patients can undergo salvage transplantation regardless of whether they have already been listed before ARF. ECMO is not able to reverse the poor prognosis in patients that do not qualify for lung transplantation.

predamaged pulmonary parenchyma is susceptible to ventilator-induced lung injury and oxygen toxicity (7, 8). This likely triggers further disease progression (9, 10). Right ventricular dysfunction is very common. Hypoxemia also leads to increased hypoxemic pulmonary vasoconstriction. Furthermore, the increase in thoracic pressure caused by mechanical ventilation adds to the right ventricular afterload elevation. Ventilation strategies commonly used for patients with acute respiratory distress syndrome have failed in these settings (11).

The use of inadequate positive end-expiratory pressure (PEEP) is linked to a further loss of pulmonary compliance resulting in the need for increased plateau pressures. High initial PEEP is an independent predictor for mortality in this group of patients (2). Besides the poor prognosis of the underlying disease, mechanical ventilation contributes to the high mortality (70–90%) following intubation. In patients on extracorporeal membrane oxygenation (ECMO), oxygen supply and decarboxylation are mainly separated from mechanical ventilation. This enables lung protective ventilation and might prevent ventilator-induced lung injury and further right ventricular dysfunction. ECMO has not yet been investigated in patients with ARF based on pulmonary fibrosis. This study is the result of a retrospective analysis of our experience with ECMO therapy in ARF based on ILD.

Methods

Study Subjects

From a computerized database, we retrieved all patients with ILD meeting American Thoracic Society/European Respiratory Society Consensus Criteria (12–14) and ARF admitted to our ICU or intermediate care ward at the University Hospital of Saarland (1,300-bed tertiary care hospital) from March 2012 to August 2015. ARF was defined as clinical evidence of respiratory distress (tachypnea, dyspnea) and hypoxemia at supplementary oxygen rates greater than or equal to 10 L/min (high-flow oxygen or NIV) or mechanical ventilation.

Forty patients fulfilled the previously mentioned criteria. We excluded three patients from the analysis because of concomitant pulmonary malignancy. Out of 37 patients, 21 were placed on ECMO. Sixteen patients not treated on ECMO for the previously mentioned reasons are not included in the following analysis (Figure 1). For information on patients not on ECMO, see the online supplement.

Acute exacerbations of ILD were defined according to Collard and colleagues (15) even if the cause of ILD was not idiopathic. The diagnosis of infectious origin was based on the presence of new or progressive infiltrates on chest radiograph and at least two of the following: (*1*) fever, (*2*) blood leukocytosis/leukopenia and/or elevated markers of infection (C-reactive protein, procalcitonin), (*3*) purulent secretions from bronchoscopy, or (*4*) positive microbiological cultures. The diagnosis of severe sepsis or septic shock was made according to the S-2k guidelines of the German Sepsis Society (16). After ICU discharge, the patients were mainly followed by a pneumologist at the lung transplant center.

The study was approved by the institutional review board (Ärztekammer des Saarlandes) with number 85/15. The necessity of informed consent was waived by the institutional review board because of the retrospective nature of the study.

ECMO Deployment

ECMO in ILD was considered in patients with severe respiratory failure if two intensivists agreed on a potentially reversible cause for deterioration (e.g., infection or pulmonary embolism) and if the patient agreed despite not being a transplant candidate or if the patient was considered to be a lung transplant candidate. ECMO was refused for patients with advanced underlying disease without transplant option and for those with a poor prognosis because of comorbidities. External cannulation and ECMO retrieval followed the same criteria; however, in time-critical situations decisions were generally made in favor of life-sustaining actions. Not all patients initially considered to be transplant candidates could be finally enlisted for lung transplantation.

ECMO was initiated if the pH was below 7.20 for respiratory causes despite mechanical ventilation with high peak and plateau pressures, generally, peak and plateau pressures higher than 35 cm H_2O. Awake ECMO was initiated to prevent intubation in patients that were hypoxemic despite high F_{IO_2} (in cases of high-flow oxygen application, calculation according to Reference 17) and physically exhausted ("at risk of intubation"); "no intubation" was denoted when ECMO was initiated. To calculate time from intubation to ECMO, awake ECMO was set to 0 days.

All patients were primarily treated with venovenous ECMO using the femoral (draining) and jugular (return) veins as standard cannula entry sites. Usually, we used 23F catheter draining cannulas and 19F catheter returning cannulas (Maquet, Rastatt, Germany) with a heparin coating. Cannulation was done percutaneously under ultrasound guidance by the staff intensivists. As standard oxygenator, a 7.0 L-HLS or Quadrox-I primed with physiologic saline solution on the Maquet CardioHelp platform (Maquet, Rastatt, Germany) was used. All tubings were 3/8 inch. The ECMO circuits and oxygenators were visually checked for clots on a daily basis. Sedation was administered according to a protocol. Daily interruption of sedation was mandatory, except in hemodynamically unstable patients. The hemodynamic situation was monitored using an arterial line and pulmonary artery catheter when appropriate. Patients were

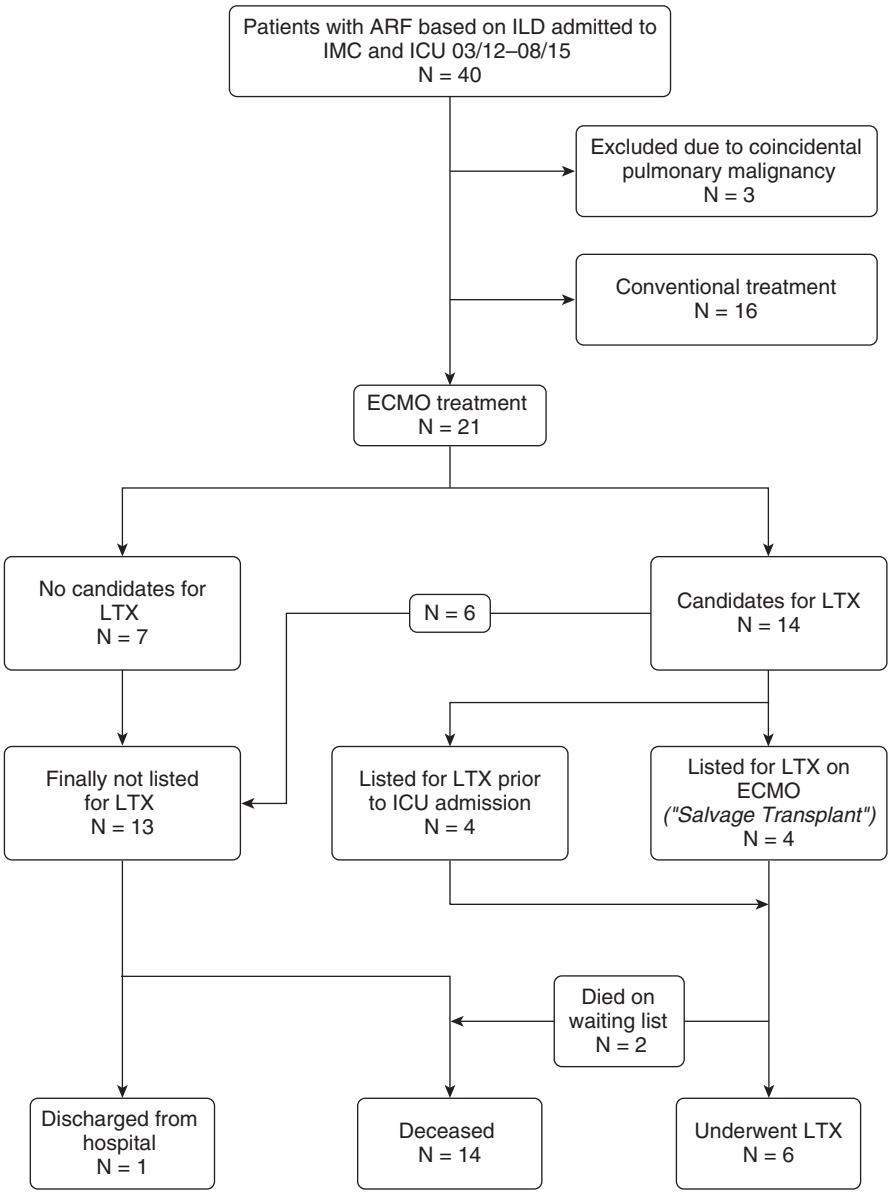

Figure 1. Consort flow chart demonstrating all patients included in this analysis. Twenty-one patients treated on extracorporeal membrane oxygenation were included in the final analysis. ARF = acute respiratory failure; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; ILD = interstitial lung disease; IMC = intermediate care ward; LTX = lung transplant.

weaned off vasopressors and sedation whenever possible. Patients previously intubated and mechanically ventilated underwent tracheostomy, if extubation and awake ECMO was not possible.

Lung Transplantation

Generally, patients were listed for lung transplantation after a structured critical review of all data by our institutional lung transplantation board in a conference including the patients' history and charts, examination and evaluation of comorbidities, discussion with patients and previously treating physicians, and after informed consent of the individual. Salvage transplantation (in a narrow sense) is used here for patients with ILD that were not listed before ARF. Patients were listed for salvage transplantation if they were placed on awake and nonintubated ECMO or were awake and able to consent during the course of ICU therapy. Patients were listed only if the institutional lung transplant board consisting of at least two transplant team physicians and one designated independent physician agreed and signed a consensus document. Organs were allocated via Eurotransplant (Leiden, The Netherlands). All donor lungs fulfilled standard criteria. Transplantation was done with cardiopulmonary bypass in case of additional pulmonary hypertension.

Statistical Analysis

Statistical analysis was performed using SPSS version 21 (SPSS Inc., Chicago, IL). Data are described by frequencies and percentages and analyzed using Kolmogorov-Smirnov to test for normal distribution. Differences between groups were analyzed using Mann-Whitney *U* test, Student's *t* test, chi-square test, and log-rank test, as appropriate. Values are reported as median ± interquartile range (IQR) and mean ± SD or mean ± SD alone. Results were considered statistically significant for *P* values less than 0.05.

Results

From March 2012 to August 2015, a total of 16 patients were treated without ECMO and 21 patients with ILD and ARF were treated with ECMO. The most frequent ILD etiology in these patients was idiopathic (7 of 21; 33.3%) followed by connective tissue disease (5 of 21; 23.8%). The final diagnosis was made with histopathologic confirmation in 14 of 21 (66.7%) of the cases. This confirmation could be either derived from open lung biopsy, from the explanted lung in cases of transplant patients, or from autopsy. The general characteristics of these patients are shown in Table 1. Patients with and without ECMO are compared in Table E1 in the online supplement.

Reasons for deterioration were mainly ILD exacerbations (n = 11 of 21) and infection/sepsis (n = 6 of 21), accounting for 17 of 21 (81.0%) of the cases. The other 4 of 21 (19.0%) had pneumothorax, deteriorated after open lung biopsy (n = 2), or had pulmonary hemorrhagia under acetylic acid and clopidogrel (Table 2).

Patients without clinical signs of infection (52.4%) received high-dose steroids (250–1,000 mg methylprednisolone for a period of 3–5 d). Three patients

Table 1. General Characteristics of Patients on ECMO Admitted to ICU

Patient Characteristics	n/N (%) or Median (IQR; Mean ± SD)
Age, yr	55.8 (50.6–64.6; 56.3 ± 11.7)
Male	15/21 (71.4)
Clinical presentation	
Previous cardiovascular disease	9/21 (42.8)
Previous pulmonary hypertension	9/21 (42.8)
SAPS II on admission	34 (27–42; 34 ± 11)
TISS-28	15 (10–17.5; 16 ± 8)
OI ($Pa_{O_2}/F_{I_{O_2}}$)	68 (50–106; 84 ± 43)
Ventilation before ECMO, d	7 (2–15.5; 8.85 ± 7.1)
ILD subgroups	
Toxic	**2/21 (9.5)**
Drug-induced	2/21 (9.6)
Connective tissue disease	**5/21 (23.8)**
Scleroderma	1/21 (4.8)
Dermatomyositis	1/21 (4.8)
Rheumatoid arthritis	1/21 (4.8)
Antisynthetase syndrome	1/21 (4.8)
Idiopathic interstitial pneumonia	**7/21 (33.3)**
IPF	3/21 (14.3)
NSIP	2/21 (9.6)
AIP	2/21 (9.6)
ILD caused by inhaled substances	**3/21 (14.3)**
Organic	1/21 (4.8)
Anorganic	2/21 (9.6)
GvHD	1/21 (4.8)
Unclassified	1/21 (4.8)
Histopathologic diagnosis	14/21 (66.7)

Definition of abbreviations: AIP = acute interstitial pneumonia; ECMO = extracorporeal membrane oxygenation; GvHD = graft-versus-host disease; ICU = intensive care unit; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; IQR = interquartile range; NSIP = nonspecific interstitial pneumonia; OI = oxygenation index (before ECMO deployment); SAPS = Simplified Acute Physiology Score; TISS-28 = Therapeutic Intervention Scoring System-28.
Values for superordinate categories are given in bold. ILD was grouped according to histopathology or American Thoracic Society/European Respiratory Society Consensus Criteria of the Idiopathic Interstitial Pneumonias (12, 14).

received cyclophosphamide rescue therapy, and one patient was treated with rituximab. Thirteen patients (61.9%) received continuous venovenous hemodialysis, and most patients were at least partially on vasopressor support (95.2%). All patients received at least one antimicrobial substance during the ICU stay. Before ECMO, 6 of 21 (28.6%) of the patients received high-flow oxygen at a median flow of 27.5 L/min (IQR, 16–30; mean, 26.4 ± 7.9 L/min) resulting in calculated $F_{I_{O_2}}$ rates up to 95% (Table 3).

Table 2. Reasons for Deterioration of ILD

	n/N (%)
ILD exacerbation	11/21 (52.4)
Infection (pneumonia)	6/21 (28.6)
Pneumothorax	1/21 (4.8)
Open lung biopsy	2/21 (9.6)
Diffuse pulmonary hemorrhagia	1/21 (4.8)

Definition of abbreviation: ILD = interstitial lung disease.
Diagnosis of ILD exacerbation was made in analogy to Reference 15.

Patients went on ECMO for different reasons. Patients that were previously mechanically ventilated were placed on ECMO with hypoxemic ventilatory failure and severe respiratory acidosis in high or very high ventilator settings (generally, peak and plateau pressures >35 cm H_2O; highest plateau pressure >55 cm H_2O; median pH, 7.18 [IQR, 7.11–7.23; 7.17 ± 0.14]). Patients that were placed on ECMO while awake and nonintubated were at risk for intubation. These patients had severe hypoxemia (median P_{O_2}, 50.4 mm Hg [IQR, 40.9–73; 55.2 ± 15.8 mm Hg]) at a median oxygenation index of 59.5 (IQR, 51.6–84.6; 65.7 ± 18.7) despite high-flow oxygen at a respiratory rate of 36 ± 6 per minute. As a consequence, pH in these patients was 7.46 (7.37–7.52; 7.43 ± 0.07). The mean P_{CO_2} was 49.0 ± 9.1 mm Hg.

Table 3. General Treatment on ICU

	n/N (%)
Vasopressor support	20/21 (95.2)
Antimicrobial agents	21/21 (100)
High-flow oxygen supplementation	6/21 (28.6)
CVVHD	13/21 (61.9)
Steroids (high-dose)	11/21 (52.4)
Cyclophosphamide	3/21 (14.3)
Rituximab	1/21 (4.8)

Definition of abbreviations: CVVHD = continuous venovenous hemodialysis; ICU = intensive care unit.

Although all patients were cannulated venovenous when placed on ECMO, the circuit was changed because of progressive right ventricular failure to venovenoarterial (n = 3) and later to total cardiopulmonary bypass (n = 2).

Fourteen patients (66.7%) were transferred to us from other ICUs. Intubated patients were median 7 days (IQR, 2–15.5; mean, 8.85 ± 7.10 d) under mechanical ventilation before ECMO support. ECMO was deployed in-house in 13 cases; eight patients were transferred with ECMO from other hospitals (seven by our mobile ECMO team). These patients with ILD were already intubated and mechanically ventilated when our center was asked to continue therapy. After an in-house review process involving the lung transplant team, the mobile ECMO team of our department cannulated and started the ECMO circuit externally. After a brief phase of stabilization, all patients were transported by air to our hospital.

Complications associated during the ECMO run were primarily bleeding and, to a much lesser extent, cannulation. These accounted for complications in 5 of 21 (23.7%) of the patients. Information on ECMO and its complications is given in Table E2.

Five external patients accepted as transplant candidates were finally not listed (*see* online supplement). Of all patients with ILD placed on ECMO, eight (50%) were listed for lung transplant (Table 4). The mean lung allocation score for all patients on ECMO was 92.1 ± 2.3 points.

Table 4. Characteristics of Patients on ECMO Enlisted for Lung Transplantation

Lung Transplantation	n/N (%) or Median (IQR; Mean ± SD)
Male	5/8
Mean age	53.1 (49–56.9; 50.6 ± 10.1)
Listed for LTX	
Before ICU admission	4/8 (50)
On ECMO (salvage transplant)	4/8 (50)
LAS	91.60 (90.25–94.55; 92.14 ± 2.28)
Waiting time on ECMO	42 (28–52; 37.0 ± 19.8)
CVVHD initiated on ICU	5/8 (55.6)
Dialysis at discharge	1/5 (29)
Mortality	4/8 (50)

Definition of abbreviations: CVVHD = continuous venovenous hemodialysis; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IQR = interquartile range; LAS = lung allocation score; LTX = lung transplant.

Four patients were on the transplant list before ECMO. After critical evaluation, all patients consented to lung transplant before intubation; four external patients were listed for salvage transplant. Two patients on the waiting list before ECMO died after 9 and 63 days of ECMO. Five of the six (83.3%) patients who received a transplant were discharged from hospital.

In contrast, 14 of 15 (93.3%) patients who did not receive a transplant died after median 41 days (IQR, 25–54; mean, 40.3 ± 27.8) on ECMO. In five patients, ECMO therapy was withdrawn; the other patients died because of (septic) multiorgan failure. The surviving patient was weaned from tracheostomy and discharged with NIV, mainly nocturnal. He was listed for transplantation only a few weeks after discharge and received a transplant 230 days after weaning from the device. Kaplan-Meier survival curves of this cohort are shown in Figure 2.

Discussion

We set out to investigate the role of ECMO in ILD. In this retrospective analysis, we finally included 21 patients treated on ECMO for ARF based on ILD. ECMO was initiated regardless of whether they could be candidates for lung transplant. The main finding is that patients with ILD on ECMO that are not lung transplant candidates have a high mortality rate, comparable with the mortality rate of these patients when mechanically ventilated. Additionally, in our cohort, there is evidence that ECMO has no value in the sense of a transplant-independent outcome improvement in ILD. In contrast, patients with an option for lung transplantation benefit from ECMO therapy. The main reason for this benefit is the time gained on ECMO.

Salvage transplant, as described only recently by Hoopes and colleagues (18), is a feasible approach in this cohort as well. In this context, salvage therapy denotes lung transplantation in patients that have not been listed before ARF. Importantly, salvage transplantation opens a window for patients that are deteriorating and are not listed for lung transplant, even if hospitalized in a facility that cannot provide both ECMO and lung transplantation. These patients can be transferred on ECMO to a facility where these are both possible.

Our study has several limitations. Limitations are basically caused by the retrospective nature of the study and the low number of patients included in this work. However, acquiring higher patient numbers is difficult because ILD

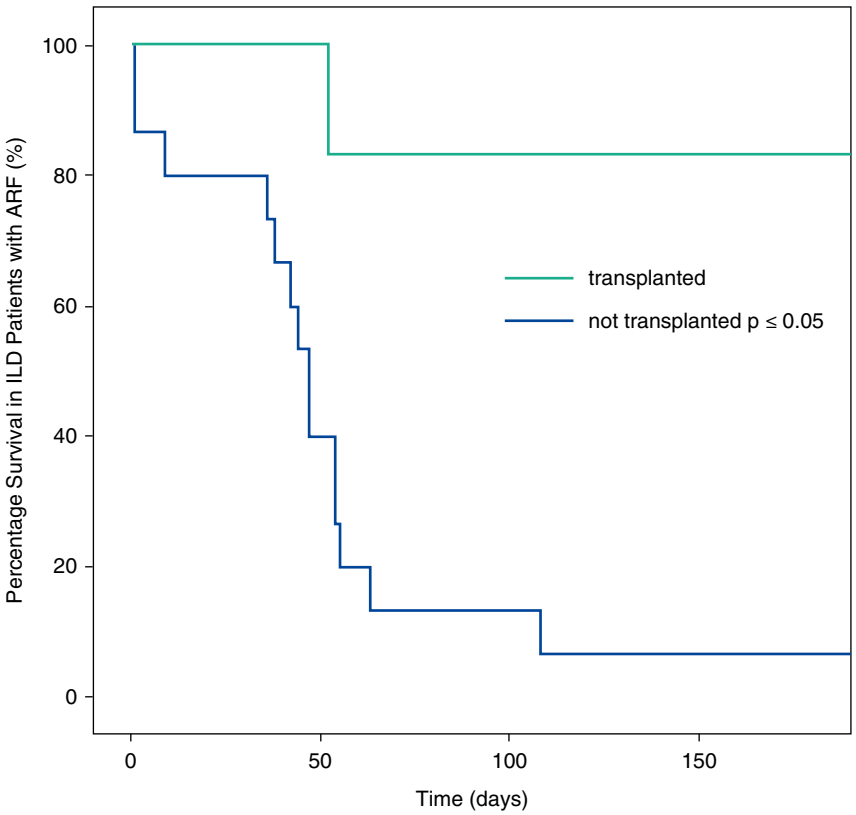

Figure 2. Kaplan-Meier survival curves of 180-day survival in patients with interstitial lung disease (ILD) with acute respiratory failure (ARF) on extracorporeal membrane oxygenation. *Blue line* (n = 15) denotes patients who did not receive transplants (including two patients that died on the waiting list). One survivor from the group not listed did finally receive a transplant. *Green line* (n = 6) denotes patients who received a transplant.

itself is a relatively rare entity, and many patients deteriorating in smaller hospitals might not be reported and transferred to larger centers. This might be caused by the widely held belief that these patients cannot be saved by intensive care measures. Although this was also true in our group of patients that were not considered transplant candidates, it might be especially difficult to judge the value of ECMO in this subgroup because these patients most likely were mechanically ventilated too long at high ventilator settings before they were placed on ECMO. Thus, it is difficult to assess the impact of ECMO in a noncontrolled retrospective study. However, patients with ILD that survived mechanical ventilation to discharge had a very limited prognosis without lung transplantation as well; 1-year survival rates were 4% (19).

Another critical issue that needs to be addressed is the lack of exact data on ventilatory support in almost all external patients before placement on ECMO. All patients were intubated in external hospitals, primarily to sustain life. We have only sparse data if high-flow oxygen or NIV was done, and if so how, before intubation and mechanical ventilation. Our decision to initiate ECMO was primarily based on pH, the last ventilator settings, and a worsening trend. In two cases, advice was given to the referring hospital to optimize ventilator settings, but the mobile ECMO team proceeded to transfer material and personnel to the patient and came to the conclusion at the bedside that the patient needed ECMO support. Also, in our ICU, ventilator settings might not have been always optimal. We used high PEEP levels to improve oxygenation and reduce ECMO flow in two patients, despite a need to use PEEP moderately in these patients (2). Retrospectively, this proved to be useless in cases other than clear infection.

However, it might be that the time from intubation to ECMO was too long. This might have led to further disease progression and might have added to the fact that ECMO could not reverse the detrimental course of ARF in ILD in our cohort. This shows, additionally, that the option of ECMO is not yet part of a therapeutic algorithm in hospitals dealing only seldom with these patients.

A general problem of lung transplantation is long wait times. This problem seems to be more prominent in the Eurotransplant area than in the United Network for Organ Sharing area, for example (18).

On a final note, intubation or ECMO in ILD might be an inevitable step if the so-called percolation threshold is reached by disease progression (20). It might well be possible that from this point on, nothing but lung transplantation can save the patient.

Conclusions

ARF in ILD is devastating in patients without the option for lung transplant, despite ECMO. Even though ECMO enables protective ventilation, patients still do not recover. ECMO seems to be an acceptable rescue tool to bridge to transplant in patients with ILD eligible for lung transplantation. Salvage transplant for these patients is possible. Patients with ARF based on ILD should be evaluated for possible transplantation. Patients with imminent NIV- or high-flow-failure who are eligible for lung transplantation but not yet listed should immediately be referred to a center with the option for both ECMO and salvage lung transplantation. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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