Lung transplantation (LTx) is a well-established therapy for patients with chronic lung failure, including interstitial lung disease, chronic obstructive pulmonary disease, cystic fibrosis, or pulmonary vascular disease. Excellent long-term survival can be achieved, making LTx a mainstay in the therapy of patients with these indications. In contrast to chronic lung diseases, the role of LTx in acute lung failure is less established. Although acute respiratory distress syndrome (ARDS) is listed as an acceptable indication by most published guidelines, there is a great variance of this practice. In general, reported numbers are low and available evidence is almost exclusively limited to case reports or small case series. With the rapid evolving SARS-CoV-2 pandemic, and an increasing number of unweanable post–COVID-19 ARDS patients receiving extracorporeal membrane oxygenation (ECMO), many LTx centers started to evaluate this practice. This work aims to summarize the currently available literature on LTx for ARDS, report outcomes of the practice of LTx for ARDS, provide guidelines of LTx for ARDS, and discuss selection criteria beyond published evidence.

SUMMARY OF PUBLISHED EVIDENCE

Several case reports on LTx for ARDS are available in the literature, with the first case published as early as 1985 by the Toronto Lung Transplant group1-9 (Table 1). The majority of these case reports describe rescue LTx, often in young patients. Underlying cause for ARDS was pneumonia in 4 patients, trauma in 3 patients, paraquat poisoning in 2 patients, and inhalation of ammonia and recombinant interleukin-2 therapy in 1 patient each. Of note, the majority of these early reports (9 out of 11 cases) highlight the evolving practice of transplantation utilizing ECMO support. To date, 3 larger case series of LTx for ARDS have been published (Table 2). The transplant group from the Asan Medical Center Seoul (in Korea) were the first to report on a cohort of 14 ARDS patients listed for LTx resulting in 9 transplantations between 2008 and 2013.10 Inhalation of humidifier disinfectant was the underlying cause of ARDS in half of these patients (7 out of 14). Of note, 3 of the 9 transplanted patients received combined heart–LTx due to postischemic left ventricular dysfunction, right-heart failure, or significant pulmonary hypertension after a previous Rashkind atrial septostomy. To date, the largest available case series is a retrospective United Network for Organ Sharing (UNOS) registry analysis performed by Harano and colleagues.11 In this publication a total of 63 ARDS patients who were listed for LTx between 2005 and 2018 were studied. Thirty-nine (61%) were ultimately transplanted, whereas 24 patients were either removed from the waiting list due to recovery or deterioration and death. The most recent report of non–SARS-CoV-2 ARDS combines the experience of 3 European high-volume centers (Vienna, Leuven, and Groningen), including 13 patients transplanted for ARDS between 1998 and 2020. In this series, viral or bacterial infection was the cause of ARDS in the majority of cases (12 out of 13).12 In addition, a recent international series focused exclusively on SARS-CoV-2–associated ARDS. It included 12 patients transplanted at
centers in the United States, Italy, Austria, and India between May and September 2020.13

REPORTED OUTCOME OF LTx FOR ARDS

Authors of all published series point out that LTx for ARDS is complex and posttransplant management is challenging. Therefore, results likely cannot be expected to reach those of standard LTx recipients. In all relevant case reports, length of mechanical ventilation (LMV) after LTx was prolonged and ranged between 17 and 34 days,2,5-8 whereas time to discharge from hospital ranged between 20 and 212 days.2-9 This is in line with results of the 3 large case series in which a median LMV of 11 to 33 days10,12,13 and a median hospital stay of 33 to 80 days were reported.10-13 These results are comparable to patients with deteriorating chronic lung diseases (eg, interstitial lung disease, cystic fibrosis, and chronic obstructive pulmonary disease), who require extracorporeal life support (ECLS) bridging and also experience prolonged LMV and hospital stays postoperatively. One single LTx patient reported by Jurmann and colleagues5 died intraoperatively. The first patient presented by the Toronto group in 1985 died from cerebral edema 3 months after transplantation.1 Iacono and colleagues4 reported recurrent pneumonia and respiratory failure as the cause of death in their patient 351 days posttransplant. All other case report patients were still alive at the time of the respective publications, with a follow-up ranging from 24 to 62 months.2,3,5-9 A similar outcome was reported in the Korean case series reported by Chang and colleagues10 who found a 1- and 3-year survival rate of 78% in their 9 patients, only 1 patient (11.1%) was died during the immediate postoperative course.10 In the European cohort, 1 patient died early after transplant, leading to an in-hospital mortality rate of 7.7%. One-year survival was 71.6% and 5-year survival 54.2%. Because this study included cases of transplant as early as 1993, an era effect could be shown. All patients undergoing transplant after 2016 were still alive at the time of publication. Harano and colleagues11 reported an in-hospital mortality rate of 10.3%, 1-year survival of 82.1%, and 3-year survival of 69.2%. This UNOS registry study also compared the ARDS group with a propensity-score matched control group of 79 LTx for restrictive lung disease.11 Matching was performed 2:1 by sex, age, and transplant type but also by lung allocation score, ensuring a control group of equal complexity. The outcomes of this matched cohort were similar to the ARDS cohort (in-hospital mortality,

### TABLE 1. Case reports

<table>
<thead>
<tr>
<th>Author</th>
<th>Year published</th>
<th>Age</th>
<th>Cause of ARDS</th>
<th>ECMO (d)</th>
<th>Tx</th>
<th>LMV</th>
<th>Hospital stay 30-d</th>
<th>90-d survival</th>
<th>1-y survival</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iacono et al</td>
<td>2009</td>
<td>24</td>
<td>Posttrauma</td>
<td>Yes (107)</td>
<td>DL</td>
<td>NA</td>
<td>212 Yes (107)</td>
<td>Yes (107)</td>
<td>No (351)</td>
<td>Failure to wean from ECMO</td>
</tr>
<tr>
<td>Salam et al</td>
<td>2017</td>
<td>55</td>
<td>Pneumonia</td>
<td>Yes (125)</td>
<td>DL</td>
<td>28</td>
<td>92 Yes</td>
<td>Yes</td>
<td>Yes (alive at 2 y)</td>
<td>Failure to wean from ECMO and MV</td>
</tr>
<tr>
<td>Licker et al</td>
<td>1998</td>
<td>17</td>
<td>Paraquat poisoning</td>
<td>No</td>
<td>SL</td>
<td>17</td>
<td>88 Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Mono-organ failure No septic state</td>
</tr>
<tr>
<td>Brichon et al</td>
<td>1993</td>
<td>32</td>
<td>1L-2 therapy</td>
<td>Yes (1)</td>
<td>DL</td>
<td>NA</td>
<td>40 Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Normal neurological function No active infection/septic state Mono-organ failure</td>
</tr>
<tr>
<td>Jurmann et al</td>
<td>1993</td>
<td>19</td>
<td>Posttraumatic</td>
<td>Yes (5)</td>
<td>DL</td>
<td>18</td>
<td>41 Yes</td>
<td>Yes</td>
<td>Yes (alive at 30 mo)</td>
<td>Mono-organ failure</td>
</tr>
<tr>
<td>Toronto LTx</td>
<td>1985</td>
<td>31</td>
<td>Paraquat poisoning</td>
<td>Yes</td>
<td>SL</td>
<td>NA</td>
<td>– Yes</td>
<td>Yes</td>
<td>No (died at 3 mo)</td>
<td>–</td>
</tr>
<tr>
<td>Barrio et al</td>
<td>2004</td>
<td>44</td>
<td>Ammonia</td>
<td>No</td>
<td>DL</td>
<td>18</td>
<td>20 Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Failure to wean from MV</td>
</tr>
<tr>
<td>Kon et al</td>
<td>2015</td>
<td>22</td>
<td>Pneumonia</td>
<td>Yes (155)</td>
<td>DL</td>
<td>NA</td>
<td>119 Yes</td>
<td>Yes</td>
<td>Yes (alive at 4 y)</td>
<td>Failure to wean from ECMO No potential for recovery</td>
</tr>
<tr>
<td>Jackson et al</td>
<td>2008</td>
<td>28</td>
<td>Pneumonia</td>
<td>Yes (28)</td>
<td>DL</td>
<td>34</td>
<td>104 Yes</td>
<td>Yes</td>
<td>Yes (alive at 5 y 2 mo)</td>
<td>No potential for recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>Pneumonia</td>
<td>Yes (10)</td>
<td>DL</td>
<td>26</td>
<td>65 Yes</td>
<td>Yes</td>
<td>Yes (alive at 3 y 11 mo)</td>
<td>Mono-organ failure</td>
</tr>
</tbody>
</table>

ARDS, Acute respiratory disease syndrome; ECMO, extracorporeal membrane oxygenation; Tx, transplant; LMV, length of mechanical ventilation; DL, double lung; NA, not available; MV, mechanical ventilation; SL, single lung; LTx, lung transplant.
9%; 1-year survival, 85.9%; and 3-year survival, 65.4%). With a median follow-up of 80 days (range, 32-160 days), the international SARS-CoV-2 series reported 11 patients (91.7%) to be alive at the time of publication with 1 death due to sepsis leading to multiorgan failure. This resulted in an in-hospital mortality of 8.3%.13 As of October 2021, more than 100 LTxs have been performed for post–COVID-19 ARDS in North America and Europe and a follow-up publication reporting long-term outcomes is eagerly awaited. Currently, no robust data are available about rates of acute rejection or chronic lung allograft dysfunction in this population.

WAITING PERIOD TO ALLOW NATIVE LUNG RECOVERY

Based on the encouraging long-term posttransplant outcome reported for patients with severe ARDS, there is meanwhile a broad consensus that LTx is a valid option for ARDS patients with irreversible damage to their native lungs, but patient selection is crucial. General criteria for LTx recipients such as normal body mass index, absence of significant comorbidities as well as recent malignancies, and adequate social support are not different to chronic indications.16 Specific criteria for ARDS patients mentioned in the literature are listed in Tables 1 and 3.

Hospital mortality of ARDS remains high, with a rate of 40% to 50%.17 Predicting the potential for lung recovery is difficult and remains a controversial issue. However, most intensive care physicians agree that sufficient time should be given to allow native lung recovery before LTx can be considered. The Extracorporeal Life Support Organization ECMO guidelines suggest to assess the potential for lung recovery after 2 weeks of ECMO.18 However, multiple case reports exist describing lung recovery, even after much extended ECMO runs extending to months.19,20 Based on recent experience with COVID-19 ARDS, we also suggest for non–COVID-19 ARDS that at the minimum 4 to 6 weeks should be allowed for a trend to manifest. Repeated chest computed tomography scans can provide guidance and distinguish reversible changes (eg, ground glass opacities) from irreversible lung parenchymal destruction or fibrosis (eg, bullous destruction or traction bronchiectasis without potential to resolve). It is important to note that lung improvement and successful ECMO wean

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### TABLE 2. Case series

<table>
<thead>
<tr>
<th>Study characteristic</th>
<th>Chang et al10 (Korean single-center)</th>
<th>Harano et al11 (United Network for Organ Sharing Database)</th>
<th>Frick et al12 (European multicenter)</th>
<th>Bharat et al13 (international multi-center)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients transplanted/listed</td>
<td>9/14</td>
<td>39/63</td>
<td>13/-</td>
<td>12</td>
</tr>
<tr>
<td>Cause of acute respiratory distress syndrome</td>
<td>Disinfectant inhalation (n = 4)</td>
<td>NA</td>
<td>Viral (n = 7)</td>
<td>Viral: SARS-CoV-2</td>
</tr>
<tr>
<td></td>
<td>Pneumonia (n = 4)</td>
<td></td>
<td>Bacterial (n = 5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Near drowning (n = 1)</td>
<td></td>
<td>Postoperative (n = 1)</td>
<td></td>
</tr>
<tr>
<td>Median recipient age (y)</td>
<td>39</td>
<td>35</td>
<td>29</td>
<td>48</td>
</tr>
<tr>
<td>Median LMV (d)</td>
<td>11</td>
<td>NA</td>
<td>33</td>
<td>16</td>
</tr>
<tr>
<td>Median hospital stay (d)</td>
<td>56</td>
<td>33</td>
<td>54</td>
<td>37</td>
</tr>
<tr>
<td>In-hospital mortality (%)</td>
<td>11.1</td>
<td>10.3</td>
<td>7.7</td>
<td>8.3</td>
</tr>
<tr>
<td>1-y survival (%)</td>
<td>78</td>
<td>82.1</td>
<td>71.6</td>
<td>NA</td>
</tr>
<tr>
<td>3-y survival (%)</td>
<td>78</td>
<td>69.2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>5-y survival (%)</td>
<td>n/a</td>
<td>NA</td>
<td>54.2</td>
<td>NA</td>
</tr>
</tbody>
</table>

SARS-CoV-2, Severe acute respiratory syndrome coronavirus type 2; LMV, length of mechanical ventilation; NA, not available.

### TABLE 3. Selection criteria

- Relative age limit <65 y depending on comorbidities
- Single organ failure of the lung, excluding transient dysfunction of liver or kidney neurological evaluation or cerebral computed tomography obligatory
- **Irreversible lung damage**
  - Without improvement in radiology
  - Radiological signs of chronic lung disease
  - Without improvement in P/F ratio, lung compliance and ECMO requirement
  - Consideration only after ≥4 wk from onset, without improvement
  - No active uncontrolled infection or septic state
  - Meet ISHLT criteria for recipient selection for listing16
  - Adequate social support for posttransplant care
  - Ability to discuss transplantation and provide consent*
  - Ability to participate in physiotherapy*

*P/F, Partial pressure of oxygen/Fraction inspired oxygen; ECMO, extracorporeal membrane oxygenation; ISHLT, International Society of Heart and Lung Transplantation. *Some exceptions can be made on case-by-case basis.
has been observed even in patients with extensive lung damage after several weeks of ECMO. Thus, the optimal time where transplantation could definitively provide a survival advantage compared with conservative management is not yet established and the indication for LTx has to be determined on an individual case basis.

THE ROLE OF COMORBIDITIES FOR THE SELECTION OF LTx CANDIDATES

Almost all publications related to LTx for ARDS discuss the relevance of single-organ failure as a major selection criterion. The importance of this is underlined by 1 of the cases presented by Jurmann and colleagues where a 32-year-old patient underwent transplant despite being in septic multiorgan failure at the time of LTx. This patient died on the operating table.5

Liver

Acute liver injury is known to severely influence mortality in patients with ARDS. Although data on the prognostic relevance of hepatic dysfunction in ECMO-bridged in LTx recipients are lacking, liver function parameters such as aspartate transaminase, alanine aminotransferase, alkaline phosphatase, serum bilirubin, and international normalized ratio should be closely monitored. Frick and colleagues reported elevated liver enzyme levels in 7 of 13 patients, corresponding to mild to moderate liver dysfunction. However, all patients had preserved coagulation.12 Because platelet dysfunction may additionally be present after long-term extracorporeal circulation, this can result in uncontrollable bleeding, especially in case of extensive pleural adhesions, which is often found in ARDS.12 Another reason for monitoring liver function parameters in this patient group is to exclude secondary sclerosing cholangitis in critically ill patients. Secondary sclerosing cholangitis in critically ill patients is rare but associated with an extremely poor prognosis, with need for liver transplantation and an elevated risk of hepatobiliary malignancies.21 Therefore, transient hepatic dysfunction may be tolerable, but excessively elevated liver enzyme levels, especially in the context of impaired coagulation, should be considered a contraindication for LTx.

Kidney

Renal function impairment is not uncommon during the course of ECMO runs.22 One patient (11.1%) in a Korean cohort10 required renal replacement therapy at the time of transplantation and 3 patients in the European cohort had an episode of kidney failure during the waiting time but fully recovered their kidney function by the time of transplantation.12 Because adequate fluid management is crucial in patients bridged to transplantation, the indication for continuous renal replacement therapy should be set liberally. In case of normal kidney function before intensive care unit admission, a temporary need for renal replacement therapy should not be a contraindication for LTx.

Heart

Patients should have cardiac evaluation in a similar fashion to other transplant candidates. Echocardiogram and coronary angiogram (for patients older than age 40 years) are recommended. Significant valvular disease or coronary artery disease would be a contraindication for transplantation in this population given their overall increased risk. Right ventricular dysfunction is common and normally would improve after transplantation.

Age

In general, ARDS LTx recipient age tends to be low, with a median of 24 years in available case reports and mean ages of 29.2 years in the European,35 years in the UNOS, and 39 years in the Korean cohorts. In recent years, the practice of accepting recipients older than age 65 years for LTx has become increasingly common and an absolute age limit for LTx does not generally exist anymore. As with other LTx indications, biological age, comorbidities, functional reserve, and muscular status, rather than a strict chronological age limit, should be focused on. During an often long intensive care unit stay before listing, functional status and frailty are key selection criteria in ARDS LTx candidates. However, to date no objective parameters exist to measure frailty, functional reserve, or the rehabilitation potential in sedated patients. Most centers use an age limit of 65 years to consider an ARDS patient to be listed. In a recent COVID-19–ARDS study age ranged from 18 to 66 years.

Sedated Versus Awake

Sedated or awake management of potential LTx candidates is an important but controversial issue. Two major strategies exist. Many centers have decided to accept sedated patients. They waive individual consent of the recipient and allow next-of-kin consent. Because thorough neurological evaluation of the LTx candidate is often impossible in this situation, cranial computed tomography is considered the obligatory minimum to assess patient neurology. A sedated bridging strategy avoids potential destabilization of the patient by aggressive weaning from MV. However, the ethical aspects of transplantation without individual informed consent and a detailed discussion of the influence and prognosis of LTx remain challenging and controversial. For these reasons, some centers only consider awake patients who are able to personally consent to transplantation. In addition, awake bridging also facilitates physical therapy and rehabilitation to counteract sarcopenia. This has been shown to improve outcomes after LTx in patients with prolonged ECMO bridging.21 Weaning from
sedation is sometimes not possible for several reasons, including patient–ventilator asynchrony and hypoxemia. Moreover, waiting for a patient to be completely weaned off sedation and able to consent carries the risk of missing the narrow window of opportunity where a patient may still be transplantable. In patients with ARDS, bacteremia/sepsis, ECMO-related, or other complications can occur anytime and render the patient nontransplantable.

**CENTER EXPERIENCE**

Large center volume has been previously associated with better outcomes for complex groups such as ECMO bridging patients.24 High volume ECMO bridge-to-transplant centers (>15 cases/year) and medium volume (>6 cases/year) had significantly better outcomes compared with <6 cases/year centers. Thus, because the perioperative as well as surgical management of ARDS recipients can be exceedingly challenging, LTx should only be performed at experienced, high-volume centers routinely transplanting ECLS-bridged patients. Centralization of these complex patients in a hub-and-spoke model should be considered.

**SURGICAL CONSIDERATIONS**

Transplanting ARDS patients is surgically challenging and in several aspects more complex compared with other indications. A bilateral LTx should be the preferred option because almost always there is bacterial colonization/super-infection in destroyed and necrotic parts of both native lungs. A single LTx approach would lead to an unacceptably high risk of sepsis in an immunosuppressed patient. In addition, many patients will also have secondary pulmonary hypertension related to the lung injury, which also favors bilateral LTx.

The need for a bilateral approach is complicated by the often substantial intraoperative blood loss. Dense and vascular pleural adhesions due to the inflammatory process are usually encountered when entering the chest. In addition, dissection of hilar structures can be difficult due to hypervascularized lymph nodes around the vessels and bronchi. Furthermore, the tissue quality of the destroyed lungs is typically fragile and adds to the surgical difficulty. Therefore, meticulous hemostasis is paramount after recipient pneumonectomy has been completed.12,13 This can be particularly challenging in the setting of previous prolonged ECLS bridging with often impaired coagulation. For these reasons, adequate surgical access is essential. We believe that a transverse bilateral thoracosternotomy (also know as a clamshell incision) is preferred over sternal-sparing approaches. This access provides excellent exposure to both pleural cavities and all relevant mediastinal structures. Intraoperative venoarterial ECMO is indispensable during LTx for ARDS. Because patients are usually on venovenous ECMO support before the transplantation, there are several options for managing intraoperative cannulation.25 Central venoarterial ECMO is the configuration of choice because peripheral venoarterial ECMO can lead to poor central oxygenation when pulmonary gas exchange is minimal. We do not recommend performing these transplants on venovenous ECMO because usually these patients have significant secondary pulmonary hypertension and some degree of right ventricular dysfunction. Furthermore, the use of cardiopulmonary bypass should be avoided in this population due to much increased risk of bleeding complications, transfusions, renal dysfunction, and primary graft dysfunction when compared with venoarterial ECMO. We advocate an intraoperative zero-heparin or low-dose heparin (anticoagulation time around 160 seconds) strategy because blood loss is often high in patients with ARDS.

After implantation, if the grafts are working well and the patient is hemodynamically stable, he or she can be weaned from ECMO in the operating room. If primary graft dysfunction develops or is anticipated, a few extra days on venovenous or venoarterial ECMO (based on patient condition and center preference) is recommended.

**CONCLUSIONS**

ARDS has emerged as an established indication for LTx in recent years, and especially during the COVID-19 pandemic. Well-selected patients can achieve good long-term survival. These patients generally were healthy before the development of severe ARDS, with a short period of severe critical illness, and have remarkable rehabilitation potential. Given the lack of treatment alternatives and the limited prognosis of some patients, LTx should be actively considered in the treatment algorithm of ARDS for patients who remain in single organ failure with signs of irreversible lung injury. However, the transplant procedure itself as well as perioperative management is complex. Therefore, LTx for patients with ARDS should only be considered in experienced centers.

**Conflict of Interest Statement**

The authors reported no conflicts of interest.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

**References**


**Key Words**: lung transplantation, ARDS, COVID-19