OPEN ACCESS
OPUS AUGSBURG

Universität Augsburg
Universitätsbibliothek

Clinical relevance of lung transplantation for COVID-19 ARDS: a nationwide study

Christian Lang, Valentin Ritschl, Florian Augustin, Gyoergy Lang, Bernhard Moser, Shahrokh Taghavi, Gabriella Murakoezy, Christopher Lambers, Holger Flick, Markus Koestenberger, Roxane Brooks, Tina Muhr, Johann Knotzer, Daniel Mydza, Marc Kaufmann, Thomas Staudinger, Christian Zauner, Claus Krenn, Eva Schaden, Andreas Bacher, Bernhard Rössler, Peter Faybik, Edda Tschernko, Maria Anwar, Klaus Markstaller, Daniel Hoefer, Tanja Stamm, Peter Jaksch, Konrad Hoetzenecker

Angaben zur Veröffentlichung / Publication details:

Lang, Christian, Valentin Ritschl, Florian Augustin, Gyoergy Lang, Bernhard Moser, Shahrokh Taghavi, Gabriella Murakoezy, et al. 2022. "Clinical relevance of lung transplantation for COVID-19 ARDS: a nationwide study." *European Respiratory Journal* 60 (3). https://doi.org/10.1183/13993003.02404-2021.

Nutzungsbedingungen / Terms of use: **CC BY 4.0**

Dieses Dokument wird unter folgenden Bedingungen zur Verfügung gestellt: / This document is made available under these conditions:
CC-BY 4.0: Creative Commons: Namensnennung
Weitere Informationen finden Sie unter: / For more information see:
https://creativecommons.org/licenses/by/4.0/deed.de

Clinical relevance of lung transplantation for COVID-19 ARDS: a nationwide study

Christian Lang[1], Valentin Ritschl[2,3], Florian Augustin[4], Gyoergy Lang[1], Bernhard Moser[1], Shahrokh Taghavi[1], Gabriella Murakoezy[1], Christopher Lambers[5], Holger Flick[6], Markus Koestenberger[7], Roxane Brooks[8], Tina Muhr[9], Johann Knotzer[10], Daniel Mydza[11], Marc Kaufmann[12], Thomas Staudinger[13], Christian Zauner[14], Claus Krenn[15], Eva Schaden[15,16], Andreas Bacher[17], Bernhard Rössler[18], Peter Faybik[19], Edda Tschernko[20], Maria Anwar[20], Klaus Markstaller[21], Daniel Hoefer[22], Tanja Stamm[2,3], Peter Jaksch[1] and Konrad Hoetzenecker[1]

[1]Dept of Thoracic Surgery, Medical University of Vienna, Vienna, Austria. [2]Section for Outcomes Research, Center for Medical Statistics, Informatics and Intelligent Systems, Medical University of Vienna, Vienna, Austria. [3]Ludwig Boltzmann Institute for Arthritis and Rehabilitation, Vienna, Austria. [4]Dept of Visceral, Transplant and Thoracic Surgery, Medical University of Innsbruck, Innsbruck, Austria. [5]Dept of Pneumology, Ordensklinikum Linz Elisabethinen Hospital, Linz, Austria. [6]Division of Pulmonology, Medical University of Graz, Graz, Austria. [7]Dept of Anaesthesiology and Intensive Care, Klinikum Klagenfurt am Wörthersee, Klagenfurt am Wörthersee, Austria. [8]Intensive Care Unit 1, Clinic of Anaesthesiology and Intensive Care Medicine, Johannes Kepler University Linz, Linz, Austria. [9]Intensive Care Unit, Division of Cardiology, Dept of Internal Medicine, State Hospital (LKH) Graz II, Graz, Austria. [10]Dept of Anaesthesiology and Critical Care Medicine, Klinikum Wels – Grieskirchen, Wels, Austria. [11]1st Medical Dept, Klinik Favoriten, Vienna, Austria. [12]Dept of Anaesthesiology and Intensive Care Unit, Bozen Central Hospital, Bozen, Italy. [13]Intensive Care Unit 13i2, Dept of Internal Medicine I, Medical University of Vienna, Vienna, Austria. [14]Intensive Care Unit 13H1, Dept of Internal Medicine III, Medical University of Vienna, Vienna, Austria. [15]Intensive Care Unit 13C1, Dept of Anaesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Vienna, Austria. [16]Ludwig Boltzmann Institute for Digital Health and Patient Safety (LBI-DHPS), Medical University of Vienna, Vienna, Austria. [17]Intensive Care Unit 13C2, Dept of Anaesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Vienna, Austria. [18]Intensive Care Unit 9D, Dept of Anaesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Vienna, Austria. [19]Intensive Care Unit 13C3, Dept of Anaesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Vienna, Austria. [20]Division of Cardiac, Thoracic and Vascular Anaesthesia and Intensive Care, Medical University of Vienna, Vienna, Austria. [21]Dept of Anaesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Vienna, Austria. [22]Dept of Cardiac Surgery, Medical University of Innsbruck, Innsbruck, Austria.

Corresponding author: Konrad Hoetzenecker (konrad.hoetzenecker@meduniwien.ac.at)

Shareable abstract (@ERSpublications)
Lung transplantation offers excellent midterm outcomes and should be incorporated in the treatment algorithm of post-COVID-19 ARDS patients https://bit.ly/33Djghz

Cite this article as: Lang C, Ritschl V, Augustin F, *et al*. Clinical relevance of lung transplantation for COVID-19 ARDS: a nationwide study. *Eur Respir J* 2022; 60: 2102404 [DOI: 10.1183/13993003.02404-2021].

Copyright ©The authors 2022.

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Received: 3 Sept 2021
Accepted: 13 Jan 2022

Abstract

Background Although the number of lung transplantations (LTx) performed worldwide for coronavirus disease 2019 (COVID-19)-induced acute respiratory distress syndrome (ARDS) is still low, there is general agreement that this treatment can save a subgroup of the most severely ill patients with irreversible lung damage. However, the true proportion of patients eligible for LTx, the overall outcome and the impact of LTx on the pandemic are unknown.

Methods A retrospective analysis was performed using a nationwide registry of hospitalised patients with confirmed severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection admitted between 1 January 2020 and 30 May 2021 in Austria. Patients referred to one of the two Austrian LTx centres were analysed, and grouped into patients accepted and rejected for LTx. Detailed outcome analysis was performed for all patients who received a LTx for post-COVID-19 ARDS and compared with patients who underwent LTx for other indications.

Results Between 1 January 2020 and 30 May 2021, 39 485 patients were hospitalised for COVID-19 in Austria. 2323 required mechanical ventilation and 183 received extracorporeal membrane oxygenation (ECMO) support. 106 patients with severe COVID-19 ARDS were referred for LTx. Of these, 19 (18%) underwent LTx. 30-day mortality after LTx was 0% for COVID-19 ARDS transplant recipients. At a median follow-up of 134 (47–450) days, 14 out of 19 patients were alive.

Conclusions Early referral of ECMO patients to a LTx centre is pivotal in order to select patients eligible for LTx. Transplantation offers excellent midterm outcomes and should be incorporated in the treatment algorithm of post-COVID-19 ARDS.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic represents a unique challenge to global healthcare. Although most patients infected with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) show a mild or even asymptomatic course, up to 30% of patients admitted to hospital require treatment in the intensive care unit (ICU) due to the development of acute respiratory distress syndrome (ARDS) [1]. In this critically ill patient cohort, unchanged high mortality rates of 30–60% have been described [1–4].

Lung transplantation (LTx) is a well-established therapeutic option for chronic end-stage lung diseases. However, it is rarely performed for acute lung failure [5] and the worldwide experience with LTx in patients with treatment-refractory ARDS is still limited. Nevertheless, long-term outcomes in patients receiving LTx for non-COVID-19 ARDS were shown to be comparable with the results of LTx for other indications [6–8]. An international consortium of six participating centres has recently reported encouraging early outcomes of 12 patients receiving LTx for COVID-19-associated ARDS and has since updated its experience with 34 cases at the Annual Meeting of the International Society of Heart and Lung Transplantation [9, 10]. Based on these reports, a consensus has been established within the transplant community that LTx can be offered for carefully selected patients suffering from irreversible ARDS due to COVID-19 [11–16]. Despite the growing number of LTx performed for post-COVID-19 ARDS, the true impact of this treatment on the pandemic and the proportion of COVID-19 ARDS patients that are eligible for LTx are unknown.

Austria was among the first countries worldwide that adopted LTx in the treatment of post-COVID-19 ARDS patients [17]. In Austria, LTx is exclusively performed in one of the two national LTx programmes (Medical University of Vienna or Medical University of Innsbruck). Notably, LTx for ARDS arising from non-COVID-19 infections (*e.g.* influenza) has been performed for several years in Austria and a nationwide referring system for ICUs has been established [8].

The aim of this study was to retrospectively summarise the management of patients with ARDS due to COVID-19 who had been considered for LTx across Austria since the beginning of the pandemic. Clinical data were evaluated for all COVID-19 patients who were admitted to hospital, received ICU treatment, and were referred and accepted for LTx due to COVID-19 ARDS. Furthermore, the clinical outcome after transplantation for COVID-19 ARDS was analysed and compared with the outcome of other transplant indications. Finally, the overall impact of offering LTx for COVID-19 ARDS cases on institutional LTx programmes was assessed.

Materials and methods

Study design and study subjects

This study was designed as a nationwide retrospective analysis covering the time period between 1 January 2020 (arbitrarily considered as the beginning of the pandemic) and 30 May 2021 (end of the third wave). The Federal Ministry of Social Affairs, Health, Care and Consumer Protection provided clinical data, including all patients with a confirmed COVID-19 infection hospitalised in Austria [18]. This dataset only included patients who were discharged from the hospital or deceased. In addition, institutional LTx databases of the Medical University of Vienna and the Medical University of Innsbruck were used to analyse COVID-19 ARDS patients referred for LTx to the two national LTx centres in Austria. These two transplant centres have the mandate to provide LTx for the entire population of Austria (currently 9 million). Based on a recent change in hospital regulations, non-Austrian residents are no longer to be considered for LTx in Austria. Patients receiving LTx for other indications during the study period were defined as the control group. The ethical committees of the Medical University of Vienna (1528/2021) and the Medical University of Innsbruck (1263/2021) approved the study protocol.

Clinical definitions

Patients were considered infected with SARS-CoV-2 if the main International Classification of Diseases, 10th Revision diagnosis upon hospital admission was “U07.1/confirmed coronavirus infection”. This definition required two positive PCR tests of nasopharyngeal swabs. Right ventricular dysfunction was registered when right ventricular hypokinesis and heightened pulmonary arterial pressure were detected in transthoracic echocardiography. Acute kidney injury was staged as 1–3 as previously defined in the recommendations of the International Society of Nephrology for adults in accordance with the Kidney Disease Improving Global Outcomes [19]. Liver dysfunction was defined as serum bilirubin >1.9 $mg \cdot dL^{-1}$

based on a definition previously published for patients with ARDS [20]. The end of mechanical ventilation was defined as extubation without early re-intubation (within 5 days). In case of re-intubation, end of mechanical ventilation was reached after the final extubation. As intermittent continuous positive airway pressure is usually part of the weaning process in tracheostomised patients, toleration of mere oxygen insufflation for >6 consecutive hours was defined as the end of mechanical ventilation.

Eight patients were referred to the two LTx centres with chronic lung diseases complicated by a COVID-19 infection during the study period and were excluded from the analysis. In general, COVID-19 ARDS patients were considered eligible for LTx in case of persistent pulmonary consolidations affecting all lobes, no radiological or clinical improvement despite mechanical ventilation or ECMO support for at least 4 weeks, negative virus culture or at least two sequential negative real-time PCR tests for SARS-CoV-2 (or cycle thresholds >32), absence of severe extrapulmonary comorbidities and potential for long-term recovery. As per our institutional policy, COVID-19 ARDS patients >65 years were not considered as suitable LTx candidates since their potential for rehabilitation from ARDS after prolonged ICU stay is low.

Statistical analysis

Continuous variables are presented as median, mean, interquartile range (IQR) or minimum–maximum range. To compare continuous variables between two or more than two groups, the t-test or ANOVA was performed, respectively. Categorical variables are presented as total numbers (percentages). Chi-squared tests were used for comparing categorical frequencies between two or more groups. If the expected frequency was <5, Fisher's exact test was applied. p-values <0.05 were considered statistically significant. All calculations and graphical illustrations were performed using Prism 8 (GraphPad, La Jolla, CA, USA), Microsoft Excel 2011 (Microsoft, Redmond, WA, USA) and R version 4.0.2 (www.r-project.org).

Results

Characteristics of COVID-19 patients requiring hospitalisation or ICU admission

Between 1 January 2020 and 30 May 2021, a total of 39 485 patients were admitted to hospital in Austria due to a confirmed COVID-19 infection. Of these 39 485 patients, 6408 were admitted to the ICU, 2323 required mechanical ventilation and 183 received ECMO support. In total, 106 patients were referred to one of the two Austrian LTx centres to assess the necessity/possibility for a LTx (figure 1). Detailed clinical data of all patients are shown in supplementary table S1.

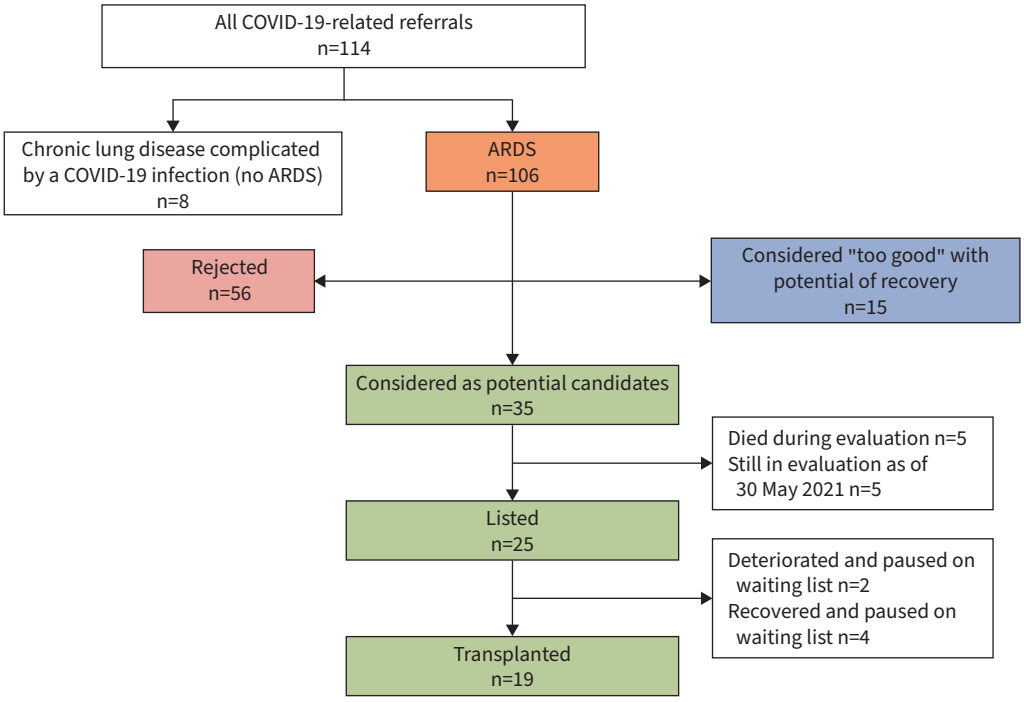

FIGURE 1 Flowchart of all COVID-19 acute respiratory distress syndrome (ARDS) patients referred to the two Austrian lung transplant centres between 1 January 2020 and 30 May 2021.

Dynamic evolution of COVID-19 hospitalisations and referrals for LTx

The dynamic evolution of the COVID-19 pandemic in Austria correlated well with the number of LTx referrals and the number of LTx performed for post-COVID-19 ARDS (figure 2). The highest numbers of hospital admissions were recorded in April 2021, November 2020 and December 2020. Consequently, ICU admissions were highest in November 2020, December 2020 and April 2021 (2168, 1832 and 1559 cases, respectively). The first patient with COVID-19 ARDS who underwent evaluation for LTx was referred in April 2020, and the number of referrals increased during the second wave (December 2000–January 2021) and third wave (March 2021–April 2021). Most LTx for COVID-19 ARDS were performed in April 2021 (n=4), and in January, February and May 2021 (n=3, each).

Characterisation of COVID-19 ARDS LTx referrals

Of the 106 patients with COVID-19 ARDS who had been referred, 90 (85%) were male and the median (range) age was 58 (26–75) years. At the time of referral, median (range) length of mechanical ventilation was 35 (6–68) days. 89 (84%) patients had been on ECMO support for a median (range) duration of 27 (1–60) days. Eight (8%) patients showed signs of right ventricular dysfunction and 17 (16%) required continuous renal replacement therapy (CRRT). The median bilirubin level was 0.83 $mg \cdot dL^{-1}$, whereas 15 (14%) patients had levels >1.9 $mg \cdot dL^{-1}$. The most common contraindicating medical conditions for a LTx were severe obesity (30%), sepsis (27%) and significant coronary artery disease (12.5%) (table 1).

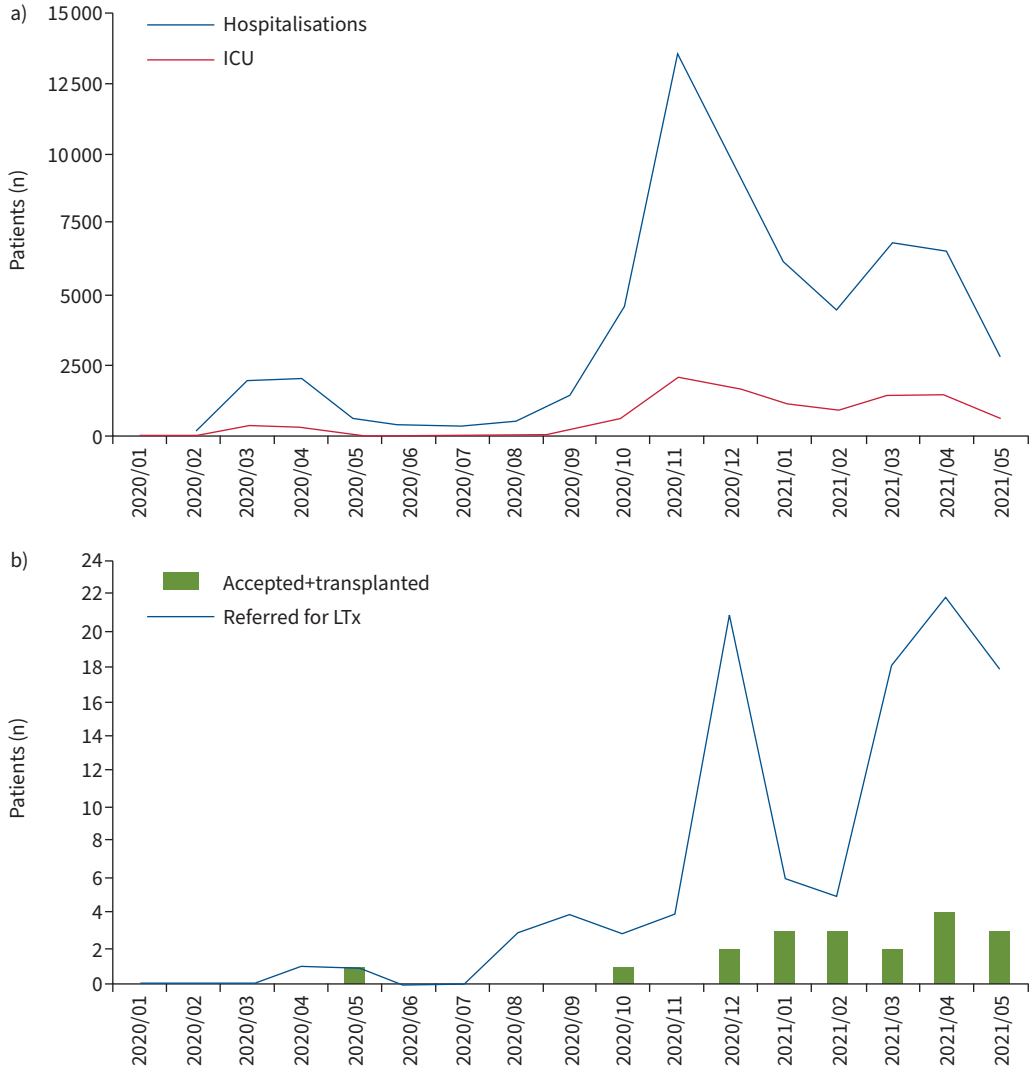

FIGURE 2 Summary of the dynamic evolution of a) COVID-19 hospitalisations and intensive care unit (ICU) referrals, and b) COVID-19 ARDS referrals for lung transplantation (LTx) and performed LTx for COVID-19 ARDS between 1 January 2020 and 30 May 2021.

TABLE 1 Descriptive data of all patients referred with COVID-19 acute respiratory distress syndrome to be considered for lung transplantation (LTx) between 1 January 2020 and 30 May 2021

	All referrals	Considered as potential candidates and underwent further evaluation	Decision against LTx		p-value
			Considered for recovery without LTx	Definitely rejected	
Patients	106 (100)	35 (33)	15 (14)	56 (53)	
Male	90 (85)	28 (80)	14 (93)	48 (86)	0.49
Age (years)	58 (26–75)	56 (34–68)	54 (39–67)	60 (26–75)	0.08
Length of MV (days)	35 (6–68)	38 (21–57)	43 (24–68)	30 (6–63)	0.0025
ECMO support	89 (84)	33 (94)	12 (80)	47 (84)	0.26
Length of ECMO support (days)	27 (1–60)	28 (3–45)	31 (24–60)	21 (1–54)	0.03
Right ventricular dysfunction	8 (8)	5 (14)	1 (7)	3 (5)	0.31
AKI stage ⩾2 during ICU stay	20 (19)	6 (17)	2 (13)	12 (21)	0.73
Renal replacement therapy	17 (16)	7 (20)	1 (6)	9 (16)	0.5
Bilirubin (mg·dL^{-1})	0.8 (0.2–12)	0.7 (0.2–7)	0.4 (0.2–5)	1 (0.2–12)	0.22
Contraindicating medical condition	58 (55)	0 (0)	2 (13)	56 (100)	<0.0001

Data are presented as n (%) or median (minimum–maximum range), unless otherwise stated. MV: mechanical ventilation; ECMO: extracorporeal membrane oxygenation; AKI: acute kidney injury; ICU: intensive care unit.

All referrals were screened by a multidisciplinary LTx team that included thoracic surgeons, transplant pulmonologists, critical care physicians and transplant psychologists. Of the 106 referred patients, 35 (33%) were considered as potential candidates (figure 1). Of these, five patients died during evaluation and five patients were still under assessment for LTx as of 30 May 2021. Consequently, 25 patients were accepted and subsequently listed for LTx. Two patients deteriorated and died while waiting for their LTx, and another four patients were paused on the waiting list due to signs of native lung recovery. Finally, 19 patients underwent LTx. Of note, median (range) time of observation (time between referral and time until decision for listing) was 14 (2–57) days. Of the 71 (67%) remaining patients, 15 (14%) were considered "too good" with a realistic chance to recover without LTx and 56 (53%) were rejected due to medical conditions not compatible with LTx. 94% of potential candidates and 100% of accepted and listed patients had been on ECMO support at the time of decision. Median (IQR) length of ECMO (28 (21–35) *versus* 21 (15–31) days; p=0.0304) and mechanical ventilation (38 (30–44) *versus* 30 (24–37) days; p=0.0025) at the time of decision differed significantly between accepted and rejected candidates. There was no difference regarding requirement of CRRT or liver dysfunction.

Surgical considerations and perioperative management of LTx

Patient characteristics and post-operative outcome of patients receiving a LTx for COVID-19-induced ARDS are provided in table 2 and supplementary table S2. Of the 19 transplanted COVID-19 ARDS patients, 16 (84%) were male and median (range) age was 56 (34–64) years. 18 patients had been bridged by veno-venous (VV) and one patient by veno-arterial (VA) ECMO support to LTx with a median (range) length of 41 (2–66) days.

All patients received a bilateral transplantation with central VA ECMO support. Due to retracted chest cavities, which are usually evident in COVID-19 ARDS patients, size reduction of the graft was performed in six (32%) cases (n=5 resection of the middle lobe and lingula, and n=1 trilobar LTx). The transplantation was usually complicated by dense pleural adhesions. In addition to this, hilar structures were often embedded in hyperinflamed lymphatic tissue, thus making hilar dissection challenging. In comparison with standard LTx, this led to a high intra-operative blood turnover and to a median (range) of 9 (2–34) packed red blood cells. Six patients had to be brought back to the operating room for haematothorax evacuation and secondary haemostasis. After LTx, four (26%) patients required prolonged VA ECMO and one (5%) patient required prolonged VV ECMO support for a median (range) length of 3 (1–5) days. Pathological assessment of the explanted lungs revealed that diffuse alveolar damage was evident across wide areas of the parenchyma in all recipients. Furthermore, acute fibrinous and organising pneumonia was seen in 13 (68%), nonspecific interstitial pneumonia in 12 (63%), multiple thromboembolism with large areas of infarction in nine (47%) and haemosiderosis in one (5%) of the explanted lungs.

LTx recipients received a pulse of corticosteroids starting intra-operatively and continuing through post-operative day 3. Maintenance immunosuppression was administered according to standard clinical

TABLE 2 Main[#] clinical characteristics and outcome of transplanted COVID-19 acute respiratory distress syndrome patients (n=19)

Patient	Age (years)	Gender	Length of MV until LTx (days)	Length of ECMO support until LTx (days)	Type of LTx	Post-operative ECMO prolongation	Length of ICU stay (days)	Discharged from hospital	Follow-up (days)	Alive/dead (cause of death)
1	44	Female	52	45	Bilateral, no size reduction	Yes	63	Yes	450	Alive
2	55	Male	29	23	Bilateral, no size reduction	No	55	Yes	300	Alive
3	54	Male	55	47	Trilobar[¶]	Yes	98	No	147	Dead (subdural haematoma)
4	57	Male	57	46	Bilateral, size-reduced[+]	No	80	No	154	Dead (liver failure)
5	61	Male	50	43	Bilateral, size-reduced[+]	No	Not reached	No	66	Dead (liver failure)
6	54	Male	39	27	Bilateral, no size reduction	No	37	Yes	207	Alive
7	49	Male	41	41	Bilateral, no size reduction	No	12	Yes	189	Alive
8	64	Male	28	17	Bilateral, no size reduction	Yes	32	Yes	180	Alive
9	56	Male	30	2	Bilateral, no size reduction	No	27	Yes	162	Alive
10	46	Female	52	52	Bilateral, no size reduction	Yes	90	No	154	Alive
11	64	Male	60	23	Bilateral, no size reduction	No	Not reached	No	111	Dead (multi-organ failure)
12	58	Male	50	8	Bilateral, no size reduction	No	25	Yes	133	Alive
13	34	Female	46	45	Bilateral, size-reduced[+]	No	25	Yes	115	Alive
14	61	Male	51	43	Bilateral, size-reduced[+]	Yes	27	No	105	Alive
15	56	Male	38	29	Bilateral, no size reduction	No	37	Yes	93	Alive
16	53	Male	76	66	Bilateral, no size reduction	Yes	Still admitted[§]	No	85	Alive
17	47	Male	38	36	Bilateral, no size reduction	No	34	No	65	Dead (liver failure)
18	62	Male	47	34	Bilateral, size-reduced[+]	No	30	No	69	Alive
19	57	Male	82	59	Bilateral, no size reduction	No	Still admitted[§]	No	47	Alive

MV: mechanical ventilation; ECMO: extracorporeal membrane oxygenation; LTx: lung transplantation; ICU: intensive care unit. [#]: more details are provided in supplementary table S2; [¶]: right upper, right lower and left upper lobe; [+]: without middle lobe and lingula; [§]: as of 11 August 2021.

practice with a FK506 (tacrolimus)-based triple immunosuppression regimen together with mycophenolate mofetil and steroids. The target trough levels of FK506 were 10–12 $ng \cdot mL^{-1}$, 1–2 g mycophenolate mofetil and steroids according to previously published institutional protocols [21].

Two female recipients were pre-LTx highly sensitised with >80% panel-reactive antibodies (due to previous pregnancies) and received pre- and post-LTx immunoadsorption in combination with rabbit antithymocyte globulin induction for 5 days (2 $mg \cdot kg^{-1} \cdot day^{-1}$ body weight). None of our patients developed any episodes of acute cellular rejection and no cases with *de novo* donor-specific antibodies or antibody-mediated rejection were detected.

Median (range) length of mechanical ventilation after LTx was 24 (4–82) days. The most common post-operative complications were critical illness polyneuropathy (79%), cholangiopathic hepatic

dysfunction (42%) and haemothorax requiring surgical revision (32%). Median (range) time until patients were able to dangle at the bedside and stand with help was 10 (5–44) and 22 (7–96) days, respectively. Patients could be transferred from the ICU to the general ward after a median (range) ICU stay of 36 (12–98) days. Patients were discharged from hospital after a median (range) of 64 (40–154) days following LTx. At the time of the analysis, the medium (range) follow-up of the 19 transplanted patients was 134 (47–450) days. Five patients died 65, 66, 111, 147 and 154 days after the transplantation. All patients had fully functioning grafts at the time of their death. Three patients died due to cholangiopathic liver failure at post-operative days 65, 66 and 154. One patient developed multi-organ failure based on recurrent infections and died on post-operative day 111. One patient had been successfully discharged and developed a massive spontaneous cerebral haemorrhage at home 21 weeks after the transplantation.

The two national LTx programmes (Medical University of Vienna and Medical University of Innsbruck) were assessed to compare outcome results of patients transplanted for COVID-19 ARDS or other indications (table 3). Overall, 156 LTx had been performed during the study period. Of these, 137 (88%) were non-COVID-19 ARDS indications. The three most common non-COVID-19 ARDS indications were emphysema (42%), interstitial lung disease (25%) and cystic fibrosis (5%). Median (range) time on waiting list was 40 (1–994) days. Despite the COVID-19-related increase of LTx during the study period, the overall waitlist mortality remained low (1.11%). Of the 156 LTx, 145 (14 COVID-19 ARDS and 130 non-COVID-19 ARDS) could be included for 3-month survival analysis. Notably, 3-month survival did not differ between COVID-19 ARDS and non-COVID-19 ARDS LTx (Fisher's exact test; p=0.1367).

Discussion

In this nationwide study, we aimed to investigate the overall relevance of LTx as a treatment option for severe COVID-19 ARDS. During the study period, 2323 COVID-19 patients required mechanical ventilation and 183 received ECMO support. The screening for LTx included a high proportion of Austrian COVID-19 patients treated by ECMO. Out of the 106 patients screened by the two lung transplant centres, 19 (18%) eventually underwent LTx. Midterm outcome of transplanted patients was encouraging, with 14 out of 19 being alive with a median follow-up of 134 (47–450) days (as of 11 August 2021).

The feasibility of LTx as an ultimate treatment option in the case of irreversible COVID-19-induced lung damage has recently been highlighted by an international multicentre study and an excellent early outcome has been reported in 12 candidates [9]. Criteria to select eligible ARDS patients for LTx were defined as: 1) negative virus status (virus culture or PCR), 2) no clinical/radiological improvement despite mechanical ventilation and/or ECMO support >4 weeks, 3) mono-organ failure (normal kidney and liver function), 4) absence of severe extrapulmonary comorbidities, and 5) a realistic potential for long-term recovery. These initial cases of "ideal" transplant candidates triggered a discussion about comorbidities that might be acceptable for a LTx and comorbidities still remaining an absolute contraindication.

An important aspect of this study is the relatively high rate of severe liver dysfunction observed after LTx. Dizier *et al*. [20] highlighted the prognostic significance of liver dysfunction in the initial phase of 805 ARDS patients. In that study, serum bilirubin >1.9 $mg \cdot dL^{-1}$ upon ICU admission was shown to represent a reliable surrogate marker for increased 90-day mortality. Focusing on COVID-19, cholangiopathy was recently shown to be a significant comorbidity and correlates with overall disease severity [22]. In our

TABLE 3 Main characteristics of the lung transplant programmes in Austria (Medical University of Vienna and Medical University of Innsbruck) between 1 January 2020 and 30 May 2021

All LTx	156 (100)
COVID-19 ARDS LTx	19 (12)
Non-COVID-19 LTx	
Emphysema (AATD/COPD)	65 (42)
Interstitial lung disease	39 (25)
Cystic fibrosis	8 (5)
Primary pulmonary arterial hypertension	4 (3)
Other	21 (13)
Time on waiting list (days)	40 (1–994)
Waitlist mortality (%)	1.11

Data are presented as n (%) or median (minimum–maximum range), unless otherwise stated. ARDS: acute respiratory distress syndrome; LTx: lung transplantation; AATD: α_1-antitrypsin deficiency; COPD: chronic obstructive pulmonary disease.

study cohort, eight (42%) of the transplanted patients developed post-operative hepatic dysfunction and three (16%) even died due to the development of severe secondary sclerosing cholangitis. These numbers are well in line with published evidence on COVID-19 ICU survivors who recovered their native lung function. According to a recent publication from a German centre, 22 out of 72 (30%) critically ill COVID-19 ICU survivors developed severe liver dysfunction [23].

Compared with non-COVID-19 LTx, early post-operative outcome was worse in COVID-19 ARDS patients. As these patients are critically ill at the time of LTx, higher early mortality can be anticipated. However, it can be assumed from the literature on LTx for non-COVID-19 ARDS that patients surviving the complex perioperative period have an excellent long-term outcome.

One of the key aspects of LTx for COVID-19 ARDS is to allow sufficient time for the native lungs to recover. Patients can only be considered for LTx in case of irreversible pulmonary damage; however, lack of reversibility is difficult to determine. Despite recent advances in ECMO, patients cannot be supported indefinitely and at a certain time-point the risk for complications increases significantly. Based on these considerations it is now recommended to wait for 6–8 weeks before listing a patient [24–26]. However, this time frame is only a rough guidance given the fact that COVID-19 ARDS patients are critically ill and clinical deterioration can occur at anytime. By strictly pursuing an 8-week hands-off period, a significant number of patients who might have been rescued by a LTx would be lost. Typical clinical scenarios that warrant an early LTx are recurrent bacterial superinfections with episodes of sepsis, necrosis of large parts of the lungs, severe pulmonary or pleural haemorrhage and recurrent tension pneumothoraces despite large bore drainages.

From an overview of an increasing number of LTx for COVID-19 (at least 100 in North America and 40 in Europe as by personal communication), it seems that two major subgroups of COVID-19-related LTx candidates can be distinguished. The first group of patients is referred to the LTx team during the acute phase of ARDS. These patients are usually deeply sedated and waking them up is often impossible. They require full circulatory/respiratory support and decision making for/against LTx takes place in a critical clinical phase. As mentioned earlier, these patients can have necrosis of their lungs or septic episodes due to pulmonary bacterial superinfection. From the surgical point of view, LTx is challenging in these patients due to destroyed anatomical structures and high intra-operative blood turnover. In addition, the post-operative rehabilitation period is often prolonged. Besides this group of severely ill patients, where LTx is more or less a rescue procedure, there is another group of patients presenting with a more chronic disease mainly characterised by fibrotic changes in their lungs. These patients are stable, awake, often able to participate in physiotherapy but cannot be weaned from ECMO or mechanical ventilation. Their overall clinical management is comparable to patients suffering from an acute deterioration of a chronic interstitial lung disease requiring extracorporeal life support bridging. Of note, during the study period, only eight (7%) of all COVID-19-related referrals (n=114) and two (1.3%) of all LTx (n=156) could be assigned to this “chronic” subgroup.

With an increasing number of lung transplant centres offering transplantation to post-COVID-19 ARDS patients, ethical concerns have been raised if the high urgency status is justified in these patients. Especially during the first wave of the pandemic, donation rates dropped dramatically, resulting in an increasing waitlist mortality for “traditional” LTx indications such as chronic obstructive pulmonary disease, interstitial lung disease, cystic fibrosis and pulmonary arterial hypertension [27, 28]. In the study period, median time on waiting list was 40 days for all LTx candidates listed in Austria. Furthermore, overall waitlist mortality was extremely low at 1.11% during the study period. Despite a temporary drop in donation rate during the first wave of the pandemic, the overall number of LTx performed in Austria remained unchanged. Moreover, we did not register an increased assessment time or time on waiting list for non-COVID-19 ARDS patients. ARDS patients who require ECMO are usually granted a high lung allocation score since their mortality without transplantation is exceptionally high. Still, 1-year survival is excellent based on the severity of their disease (85% 1-year survival according to a recent United Network for Organ Sharing analysis) [6]. Based on these considerations, COVID-19 ARDS patients are prioritised over non-COVID-19 indications.

The importance of LTx as a therapeutic option in severe COVID-19 can be best conceived by comparing the survival of COVID-19 ARDS with and without LTx. Mortality rates for severe COVID-19 ARDS (without the possibility of a rescue LTx) remain high at 30–60% [2–4]. Although long-term survival for LTx in post-COVID-19 ARDS patients is still not available, it can be assumed that 1-year survival will range between 70% and 90% based on available data of non-COVID-19 ARDS patients. Our analysis could show that a considerable number of COVID-19 patients can be saved by LTx by a nationwide LTx

referral structure. Although LTx was only an option for ∼20% of referred patients, it has the potential to reduce the overall mortality of COVID-19 disease.

Our study has several limitations that must be acknowledged. The follow-up period is still limited, therefore data on long-term survival cannot be provided. Further follow-up studies are needed to clarify the long-term survival benefit of LTx for COVID-19-induced ARDS. Although, to the best of our knowledge, this study assembles the largest cohort of LTx for COVID-19 currently available, conclusions are still limited to the small number of only 19 patients. We have recently reached out to the leading lung transplant centres in North America and Europe, and hope to provide a pooled experience of LTx for COVID-19 ARDS soon.

In conclusion, our study could demonstrate that LTx is a relevant treatment modality for severe COVID-19 ARDS. Although it is only an option for a selected group of patients, it is highly effective and has the potential to reduce COVID-19-related mortality. Centres considering LTx for COVID-19-induced ARDS should be aware of tedious recovery after the procedure requiring extensive healthcare resources. Despite these challenges, LTx for COVID-19 ARDS is feasible and early post-operative outcomes are comparable to other common chronic indications.

Conflict of interest: The authors declare that there is no conflict of interest.

References

1 Abate SM, Ahmed Ali S, Mantfardo B, *et al.* Rate of intensive care unit admission and outcomes among patients with coronavirus: a systematic review and meta-analysis. *PLoS One* 2020; 15: e0235653.
2 Armstrong RA, Kane AD, Kursumovic E, *et al.* Mortality in patients admitted to intensive care with COVID-19: an updated systematic review and meta-analysis of observational studies. *Anaesthesia* 2021; 76: 537–548.
3 Supady A, Taccone FS, Lepper PM, *et al.* Survival after extracorporeal membrane oxygenation in severe COVID-19 ARDS: results from an international multicenter registry. *Crit Care* 2021; 25: 90.
4 Biancari F, Mariscalco G, Dalén M, *et al.* Six-month survival after extracorporeal membrane oxygenation for severe COVID-19. *J Cardiothorac Vasc Anesth* 2021; 35: 1999–2006.
5 van der Mark SC, Hoek RAS, Hellemons ME. Developments in lung transplantation over the past decade. *Eur Respir Rev* 2020; 29: 190132.
6 Harano T, Ryan JP, Chan EG, *et al.* Lung transplantation for the treatment of irreversible acute respiratory distress syndrome. *Clin Transplant* 2021; 35: e14182.
7 Chang Y, Lee SO, Shim TS, *et al.* Lung transplantation as a therapeutic option in acute respiratory distress syndrome. *Transplantation* 2018; 102: 829–837.
8 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.
9 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: 487–497.
10 Machuca TN, Bharat A, Kurihara C, *et al.* International experience with lung transplantation for COVID-19 associated acute respiratory distress syndrome. *J Heart Lung Transplant* 2021; 40: S12.
11 Oh DK, Hong SB, Kim HC, *et al.* Experience of international air transportation and subsequent lung transplant in a patient with COVID-19-associated acute respiratory distress syndrome: a case report. *J Korean Med Sci* 2021; 36: e123.
12 Bharat A, Querrey M, Markov NS, *et al.* Lung transplantation for patients with severe COVID-19. *Sci Transl Med* 2020; 12: eabe4282.
13 Chen JY, Qiao K, Liu F, *et al.* Lung transplantation as therapeutic option in acute respiratory distress syndrome for coronavirus disease 2019-related pulmonary fibrosis. *Chin Med J* 2020; 133: 1390–1396.
14 Mao L, Luo L, Wang D, *et al.* Early rehabilitation after lung transplantation with extracorporeal membrane oxygenation (ECMO) of COVID-19 patient: a case report. *Ann Transl Med* 2021; 9: 512.
15 Han W, Zhu M, Chen J, *et al.* Lung transplantation for elderly patients with end-stage COVID-19 pneumonia. *Ann Surg* 2020; 272: e33–e34.
16 Cypel M, Keshavjee S. When to consider lung transplantation for COVID-19. *Lancet Respir Med* 2020; 8: 944–946.
17 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: 1057–1060.
18 Federal Ministry of Social Affairs, Health, Care and Consumer Protection. Austrian Epidemiological Reporting System: Datenplattform Covid-19. https://datenplattform-covid.goeg.at/english Date last accessed: 28 January 2021.

19 Thomas ME, Blaine C, Dawnay A, *et al.* The definition of acute kidney injury and its use in practice. *Kidney Int* 2015; 87: 62–73.

20 Dizier S, Forel JM, Ayzac L, *et al.* Early hepatic dysfunction is associated with a worse outcome in patients presenting with acute respiratory distress syndrome: a post-hoc analysis of the ACURASYS and PROSEVA studies. *PLoS One* 2015; 10: e0144278.

21 Jaksch P, Ankersmit J, Scheed A, *et al.* Alemtuzumab in lung transplantation: an open-label, randomized, prospective single center study. *Am J Transplant* 2014; 14: 1839–1845.

22 Nardo AD, Schneeweiss-Gleixner M, Bakail M, *et al.* Pathophysiological mechanisms of liver injury in COVID-19. *Liver Int* 2021; 41: 20–32.

23 Roedl K, Jarczak D, Drolz A, *et al.* Severe liver dysfunction complicating course of COVID-19 in the critically ill: multifactorial cause or direct viral effect? *Ann Intensive Care* 2021; 11: 44.

24 Schmidt M, de Chambrun MP, Lebreton G, *et al.* Extracorporeal membrane oxygenation instead of invasive mechanical ventilation in a patient with severe COVID-19-associated acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2021; 203: 1571–1573.

25 Guo F, Deng C, Shi T, *et al.* Recovery from respiratory failure after 49-day extracorporeal membrane oxygenation support in a critically ill patient with COVID-19: case report. *Eur Heart J Case Rep* 2021; 5: ytaa462.

26 Fitzgerald AL, Vachharajani HH, Davidson BP, *et al.* The prolonged use of VV ECMO support in COVID-19: a case report. *J Crit Care Med* 2020; 6: 224–230.

27 Chan EG, Chan PG, Harano T, *et al.* Trends in lung transplantation practices across the United States during the COVID-19 pandemic. *Transplantation* 2021; 105: 187–192.

28 Hardman G, Sutcliffe R, Hogg R, *et al.* The impact of the SARS-CoV-2 pandemic and COVID-19 on lung transplantation in the UK: lessons learned from the first wave. *Clin Transplant* 2021; 35: e14210.