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

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Take home message:

Lung transplantation offers excellent midterm outcomes and should be incorporated in the treatment algorithm of post-COVID-19 ARDS patients.

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Abstract

Background:

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

Methods:

A retrospective analysis was performed using a nationwide registry of hospitalized patients with confirmed severe acute respiratory syndrome coronavirus type 2 (SARS-Cov-2) infection admitted between January 1, 2020 and May 30, 2021 in Austria. Patients referred to one of the two Austrian LTx centers were analyzed 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 to patients who underwent LTx for other indications.

Results:

Between January 1, 2020 and May 30, 2021, 39.485 patients were hospitalized for COVID-19 in Austria. 2323 required mechanical ventilation, 183 received extra-corporeal 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. With a median follow-up of 134 (47-450) days, 14/19 patients are alive.

Conclusions:

Early referral of ECMO patients to a LTx center 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 COVID-19 pandemic represents a unique challenge to global health care. 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 intensive care units (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] This results in a worldwide still limited experience with LTx in patients with treatment-refractory ARDS. Nevertheless, long-term outcomes in patients receiving LTx for non-COVID ARDS were shown to be comparable with the results of LTx for other indications.[6-8] An international consortium of 6 participating centers has recently reported encouraging early outcomes of 12 patients receiving LTx for COVID-19 associated ARDS and has updated its experience with meanwhile 34 cases at the annual meeting of the International Society of Heart and Lung Transplantation.[9] 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.[10-15] 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, which adopted LTx in the treatment of post-COVID-19 ARDS patients.[16] In Austria, LTx is exclusively performed in one of the two national LTx programs (Medical University of Vienna or Medical University of Innsbruck). Notably, LTx for ARDS arising from non-COVID 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 summarize the management of patients with ARDS due to COVID-19 ARDS patients, 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, clinical outcome after transplantation for COVID-19 ARDS was analyzed and compared to the outcome of other transplant indications. Finally, the overall impact of offering LTx for COVID-19 ARDS cases on institutional LTx programs was assessed.

Materials and Methods

Study design and study subjects

This study was designed as a nationwide retrospective analysis covering the time period between January 1, 2020 (arbitrarily considered as the beginning of the pandemic) and May 30, 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 hospitalized in Austria.[17] This data set 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 analyze COVID-19 ARDS patients referred for LTx to the two national LTx centers in Austria. These two transplant centers 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 be considered for LTx in Austria. Patients receiving LTx for other indications during the study period were defined as the control group. Ethical Committees of the Medical University of Vienna (1528/2021) and Medical University of Innsbruck (1263/2021) approved the study protocol.

Clinical definitions and statistical analysis

Patients were considered infected with SARS-CoV-2 if the main ICD 10 diagnosis upon hospital admission was " U07.1 / confirmed coronavirus infection ". This definition required two positive PCR tests of nasopharyngeal swabs. Right ventricular (RV) dysfunction was registered when RV hypokinesis and heightened pulmonary artery pressure (PAP) were detected in transthoracic echocardiography. Acute kidney injury was (AKI) staged as AKI 1 to 3 as previously defined in the recommendations of the International Society of Nephrology for adults in accordance to the Kidney Disease Improving Global Outcomes.[18] Liver dysfuntion was defined as a serum bilirubin >1.9mg/dl based on a definition previously published for patients with ARDS.[19] The end of mechanical ventilation was defined as extubation without early reintubation (within 5 days). In case of reintubation, end of mechanical ventilation was reached after the final extubation. As intermittent continuous positive airway pressure is usually part of the weaning process in tra-

cheostomized patients, toleration of mere oxygen insufflation for more than 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 (MV) 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 extra-pulmonary comorbidities and potential for long-term recovery. As by 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.

Continuous variables are presented as median, mean, interquartile range (IQR) or minimum/maximum. To compare continuous variables between two or more than two groups, Student's t-test or analysis of variance (ANOVA) was performed, respectively. Categorical variables are presented with total numbers and percentages. Chi-squared tests were used for comparing categorical frequencies between two or more groups. If the expected frequency was below 5, Fisher's exact test was applied. P values below 0.05 were considered statistically significant. All calculations and graphical illustrations were performed using GraphPad Prism 8 (GraphPad Software,Inc, USA), Microsoft Excel 2011 (Microsoft Corporation, USA) and R 4.0.2 (https://www.r-project.org).

Results

Characteristics of COVID-19 patients requiring hospitalization or ICU admission

Between Jan 1, 2020 and May 30, 2021, a total of 39.485 patients were admitted to the hospital in Austria due to a confirmed COVID-19 infection. Of these 39.485 patients, 6408 were admitted to ICU, 2323 required mechanical ventilation and 183 received ECMO support. A total of 106 patients were referred to one of the two Austrian LTx centers to assess the necessity/possibility for a LTx (**Figure 1**). Detailed clinical data of all patients are shown in **Supplementary Table 1.**

Dynamic evolution of COVID-19 hospitalizations 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 performed LTx for post-COVID-19 ARDS (**Figure 2**). In April 2021, November 2020 and December 2020, the highest numbers of hospital admissions were recorded. Consequently, ICU admissions were highest in November, December 2020 and April 2021 with 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 (December 20/January 21) and third wave (March/April 21). Most LTx for COVID-19 ARDS were performed in April 2021 (n=4) and January/February/May 2021 (n=3, each).

Characterization 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 age was 58 (26-75) years. At the time of referral, median length of mechanical ventilation was 35 days (6 – 68). 89 (84%) patients had been on ECMO support for a median duration of 26 (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/dl, whereas 15 (14%) patients had levels >1.9 mg/dl. Most common contraindicating medi-

cal conditions for a LTx were severe obesity (30%), sepsis (27%) and significant coronary artery disease (12.5%) **(Table 1).**

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, 5 patients died during evaluation and 5 patients were still under assessment for LTx as of May 30, 2021. Consequently, 25 patients were accepted and subsequently listed for LTx. Two patients deteriorated and died while waiting for their LTx, another 4 patients were paused on the waiting list due to signs of native lung recovery. Finally, 19 patients underwent LTx. Of note, median 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. 56 (53%) were rejected due to medical conditions not compatible with a LTx. 94% of potential candidates and 100% of accepted and listed patients had been on ECMO support at the time of decision. Median length of ECMO (28 (IQR 21-35) vs 21 (IQR 15-31) days , p=0.0304) and mechanical ventilation (38 (IQR 30-44) vs 30 (IQR 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

Detailed patient characteristics and postoperative outcome of patients receiving a LTx for COVID-19-induced ARDS is provided in **Table 2 and Supplementary Table 2**. Of the 19 transplanted COVID-19 ARDS patients, 16 (84%) were male and median age was 56 (range 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 length of 41 days (range 2-66).

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 6 (32%) cases (5x resection of the middle lobe and lingula, 1x 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 to standard LTx, this led to a high intraoperative blood turnover and to a median of 9 (range 2-34) packed red blood cells. 6 patients had to be brought back to the OR for hematothorax evacuation and secondary hemostasis. After LTx, 4 (26%) patients required prolonged VA ECMO and one (5%) patient prolonged VV ECMO support for a median length of 3 (range 1-5) days. Pathological assessement of the of the explanted lungs revealed that diffuse alveolar damage was evident across wide areas of the parenchyma in all recipients. Furthermore, acute fibrinous and organizing pneumonia was seen in 13 (68%), non-specific interstitial pneumonia in 12 (63%), multiple thromboembolism with large areas of infarction in 9 (47%) and hemosiderosis in 1 (5%) of the explanted lungs.

LTx recipients received pulse of corticosteroids starting intraoperatively and continuing through postoperative day (POD) 3. Maintenance immunosuppression (IS) was administered according to standard clinical practice with a tacrolimus based tripe IS regimen together with mycophenolate mofetil (MMF) and steroids. The target trough levels of FK 506 were between 10-12ng/ml, 1-2g MMF and steroids according to previously published institutional protocols.[20]

Two female recipients were pre-LTx highly sensitized with more than 80% panel-reactive antibodies (due to previous pregnancies) and received pre- and post-LTx immunadsorption in combination with rabbit anti-thymocyte globulin induction for 5 days (2mg/kg body weight /day). None of our patients developed any episodes of acute cellular rejection and no cases with de novo donor specific antibodies or antibody mediated rejection was detected.

Median length of mechanical ventilation after LTx was 24 (range 4-82) days. Most common postoperative complications were critical illness polyneuropathy (79%), cholioangiopathic hepatic dysfunction (42%) and hemothorax requiring surgical revision (32%). Median time until patients were able to dangle at bedside and stand with help were 10 (5-44) and 22 (7-96) days. Patients could be transferred from ICU to general ward after a median ICU stay of 36 (12-98) days. Patients were discharged from hospital after a median of 64 (40-154) days following LTx. At the time of the analysis, the medium 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 pa-

tients had fully functioning grafts at the time of their decease. Three patients died due to cholangiopathic liver failure at POD 65, POD 66 and POD 154. One patient developed multiorgan failure based on recurrent infections and died on POD 111. One patient had been successfully discharged and developed a massive spontaneous cerebral hemorrhage at home 21 weeks after the transplantation.

To compare outcome results of patients transplanted for COVID-19 ARDS or other indications, the two national LTx programs (Medical University of Vienna and Medical University of Innsbruck) were assessed (**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, interstitial lung disease and cystic fibrosis with 42%, 25% and 5%. Median 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-months survival analysis. Notably, 3-months 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 lung transplantation 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 centers, 19 (18%) eventually underwent LTx. Mid-term outcome of transplanted patients was encouraging with 14/19 being alive with a median follow-up of 134 (47-450) days (as of August 11, 2021).

The feasibility of LTx as an ultimate treatment option in case of irreversible COVID-19-induced lung damage has recently been highlighted by an international multi-center study and an excellent early-outcome has been reported in 12 candidates.[9] Criteria to select eligible ARDS patients for LTx were defined as: i) negative virus status (virus culture or PCR) ii) no clinical/radiological improvement despite MV and/or ECMO support >4 weeks, iii) mono-organ failure (normal kidney and liver function), iv) absence of severe extra-pulmonary comorbidities, and v) a realistic potential for long-term recovery. These initial cases of 'ideal' transplant candidates triggered a discussion about comorbidities which 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 observerd after LTx. Dizier et al. highlighted the prognostic significance of liver dysfunction in the initial phase of 805 ARDS patients.[19] In this study, a serum bilirubin >1.9 mg/dL 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.[21] In our study cohort, 8 (=42 %) of the transplanted patients developed postoperative hepatic dysfunction and 3 (=16%) even deceased 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 center, 22/72 (30%) of critically ill COVID-19 ICU survivors developed severe liver dysfunction.[22]

Compared to non-COVID LTx, early postoperative outcome was worse in COVID-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 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 or 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. [23-25] 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 which warrant an early LTx are recurrent bacterial superinfections with episodes of sepsis, necrosis of large parts of the lungs, severe pulmonary or pleural hemorrhage and recurrent tension pneumothoraces despite large bore drainages.

Overlooking an increasing number of lung transplantations 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 above, 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 intraoperative blood turn-over. In addition, the postoperative rehabilitation period is often prolonged. Besides, this group of severly ill patients, where LTx is more or less a rescue procedure, there is another group of patients presenting with a more chronic disease mainly characterized by fibrotic changes in their lungs. These patients are sta-

ble, awake, often able to participate in physiotherapy but cannot be weaned from ECMO or MV. Their overall clinical management is comparable to patients suffering from an acute deterioration of a chronic interstitial lung disease (ILD) requiring extra-corporal life support bridging. Of note, during the study period, only 8 (7%) of all COVID-19 (n=114) related referrals and 2 (1.3%) of all LTx (n=156) can be assigned to this 'chronic' subgroup.

With an increasing number of lung transplant centers 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 wait list mortality for 'traditional' LTx indications such as chronic obstructive pulmonary disease, interstitial lung disease, cystic fibrosis, pulmonary arterial hypertension.[26,27] 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 with 1.11% during the study period. Despite a termorary 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 and time on the waitlist for non-COVID ARDS patients. ARDS patients who require ECMO are usually granted a high lung allocation score since their mortality without transplantation is exceptionally high. Still, one-year survival is excellent based on the severity of their disease (85% one-year survival according to a recent UNOS analysis).[6] Based on these considerations, COVID-19 ARDS patients are prioritized over non-COVID-19 indications.

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

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 this study resembles the largest cohort of LTx for COVID-19 currently available to the best of our knowledge, conclusions are still limited to the small number of only 19 patients. We have recently reached out to the leading lung transplant centers 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. Centers considering LTx for COVID-19 induced ARDS should be aware of tedious recovery after the procedure requiring extensive health care ressources. Despite these challenges, LTx for COVID-19 ARDS is feasible and early postoperative outcomes are comparable to other common chronic indications.

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Table 1 – Descriptive data of all patients who have been referred with COVID-19 ARDS to be considered for LTx between January 1, 2020 and May 30, 2021.

	All referrals	Considered as potential candidate and underwent further evaluation	Decision against LT		p-values
			Considered for recovery without LT	Definitely rejected	
Number of patients	106 (100%)	35 (33%)	15 (14%)	56 (53%)	-
Gender (male)	90 (85%)	28 (80%)	14 (93%)	48 (86%)	0.49
Age (years, median, min-max)	58 (26 – 75)	56 (34 – 68)	54 (39 – 67)	60 (26-75)	0.08
Length of MV (days, median, min-max)	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, median, min-max)	27 (1-60)	28 (3-45)	31 (24-60)	21 (1-54)	0.03
Right ventricular dysfunction	9 (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, median, min-max)	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

MV= mechanical ventilation; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; AKI = acute kidney injury;

Table 2: Main clinical characteristics and outcome of transplanted COVID-19 ARDS patients (n=19).

	#1	#2	#3	#4	#5	#6	#7	#8	#9
Age	44	55	54	57	61	54	49	64	56
Gender	female	Male	Male	Male	Male	Male	Male	Male	Male
Length of MV until LTx (days)	52	29	55	57	50	39	41	28	30
Length of ECMO support until LTx (days)	45	23	47	46	43	27	41	17	2
Type of LTx	Bilateral, no size reduction	Bilateral, no size reduction	Trilobar (right upper + right lower + left upper lobe)	Bilateral, size-reduced (without middle lobe + lingula)	Bilateral, size-reduced (without middle lobe + lingula)	Bilateral, no size reduction	Bilateral, no size reduction	Bilateral, no size reduction	Bilateral, no size reduction
Postop ECMO prolongation	Yes	no	Yes	No	No	No	No	Yes	No
Length of ICU stay	63	55	98	80	Not reached	37	12	32	27
Discharged from hospital	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Follow up (days)	450	300	147	154	66	207	189	180	162
Alive / dead (cause of death)	alive	alive	dead (subdural hematoma)	dead (liver failure)	dead (liver failure)	alive	alive	alive	alive

MV= mechanical ventilation; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; CT = computed tomography; AKI = acute kidney injury; N/A = not applicable; CIP = critical illness polyneuropathy;

	#10	#11	#12	#13	#14	#15	#16	#17	#18	#19
Age	46	64	58	34	61	56	53	47	62	57
Gender	Female	Male	Male	Female	Male	Male	Male	Male	Male	Male
Length of MV until LTx (days)	52	60	50	46	51	38	76	38	47	82
Length of ECMO support until LTx	52	23	8	45	43	29	66	36	34	59
Type of LTx	Bilateral, no size reduction	Bilateral, no size reduction	Bilateral, no size reduction	Bilateral, size-reduced (without middle lobe + lingula)	Bilateral, size-reduced (without middle lobe + lingula)	Bilateral, no size reduc-tion	Bilateral, no size reduction	Bilateral, no size reduction	Bilat-eral, size-re-duced (with-out middle lobe + lingula)	Bilateral, no size reduc-tion
Postop ECMO prolonga-tion	Yes	No	No	No	Yes	No	Yes	No	No	No
Length of ICU stay	90	Not reached	25	25	27	37	Still admitted	34	30	Still admit-ted
Discharged from hospi-tal	No	no	Yes	yes	no	yes	No	No	No	no
Follow up (days)	154	111	133	115	105	93	85	65	69	47
Alive / dead (cause of death)	alive	dead (multi-organ failure)	alive	alive	alive	alive	alive	dead (liver failure)	alive	alive

MV= mechanical ventilation; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; CT = computed tomography; N/A = not applicable; AKI = akute kidney injury; CIP = critical illness polyneuropathy; SIADH = syndrome of inappropriate antidiuretic hormone secretion

Table 3 – Main characteristics of the lung transplant programs in Austria (Medical University of Vienna and Medical University of Innsbruck) between January 1, 2020 and May 30, 2021.

Number of all LTx		156 (100%)
Number of COVID-19 ARDS LTx		19 (12%)
Non-COVID-19 LTx	Emphysema (A1ATM / COPD)	65 (42%)
	Interstitial lung disease	39 (25%)
	Cystic fibrosis	8 (5%)
	Primary pulmonary artery hypertension	4 (3%)
	other	21 (13%)
Time on waiting list (days, median, min-max)		40 (1-994)
Waitlist mortality		1.11%

Figure 1: Flow chart of all COVID-19 ARDS patients referred to the two Austrian LTx centers between January 1, 2020 and May 30, 2021. (ARDS = acute respiratory distress syndrome)

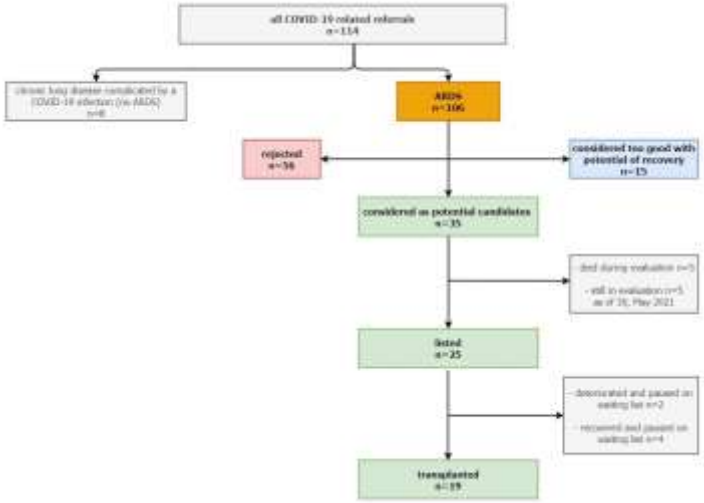
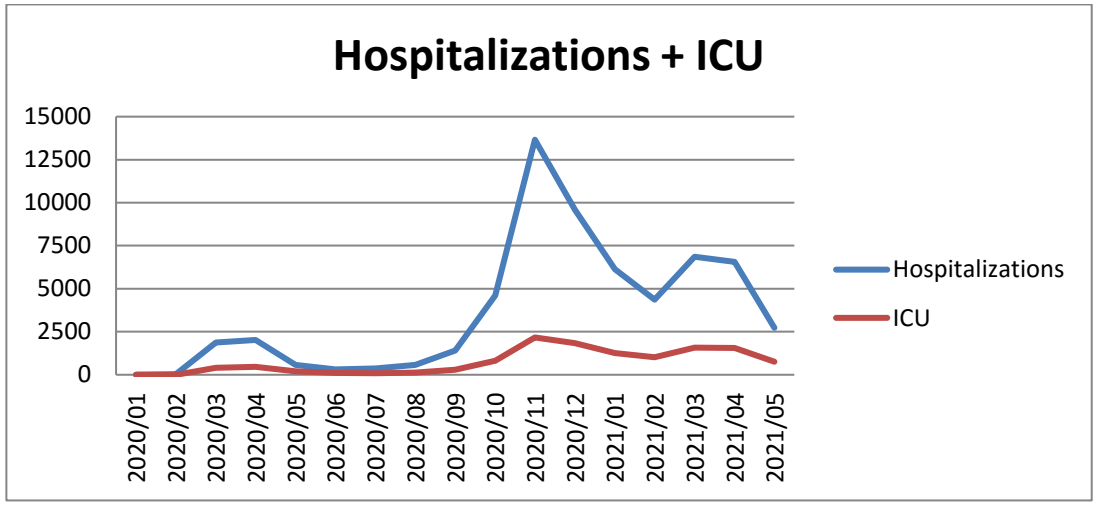
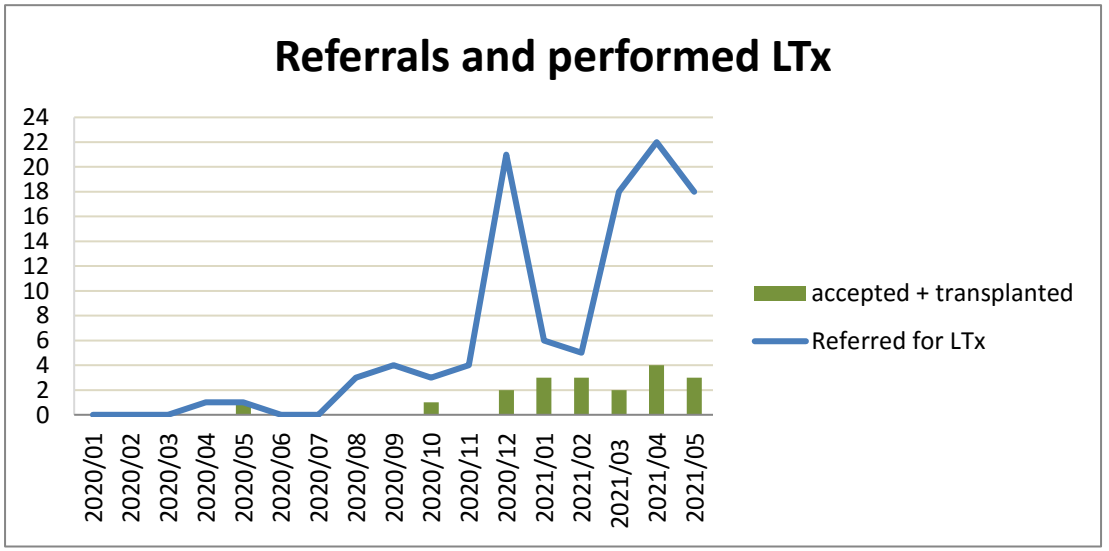


Figure 2: Summary of the dynamic evolution of COVID-19 hospitalizations, ICU referrals, COVID-19 ARDS referrals for LTx and performed LTx for COVID-19 ARDS between January 1, 2020 and May 30, 2021. (ICU = intensive care unit; LTx = lung transplantation)





Supplementary Table 1

Demographics of patients with COVID-19 infection requiring hospital and ICU admission in Austria between January 1, 2020 and May 30, 2021.

Hospitalizations		
Number of all patients		n=39485
Sex (female)		n=18129 (46%)
Age < 65 years		n=14363 (36%)
Length of hospital stay (days, median, IQR)		8 (3-18)
Referred to ICU*		n=6408 (16%)
Deceased (mortality in %)		n=7109 (18%)
ICU admissions*		
Number of all patients		n=6408
Sex (female)		n=2181 (34%)
Age < 65 years		n=2470 (39%)
Comorbidities	Hematologic disease	n=106 (1.6%)
	HIV positive	n=2 (<1%)
	AIDS	n=1 (<1%)
	Malignancy (with metastasis)	n=67 (1%)
	Malignancy (without metastasis)	n=145 (2%)
	Liver failure	n=50 (<1%)
	Heart failure NYHA II	n=518 (8%)
	Heart failure NYHA III	n=228 (4%)
	Heart failure NYHA IV	n=86 (1%)
	Chronic respiratory disease, COPD	n=548 (9%)
	Chronic renal failure	n=584 (9%)
	Alcohol abuse	n=95 (1%)
	Drug abuse	n=7 (<1%)
	Receives immunosuppressive treatment	n=129 (2%)
	Insulin-dependent diabetes mellitus type I	n=325 (5%)
	Non-insulin-dependent diabetes mellitus type II	n=800 (12%)
	Arterial hypertension	n=2586 (40%)
Mechanical ventilation		n=2323 (36%)
ECMO support		n=183 (3%)
Renal replacement therapy		n=335 (5%)
Length of ICU stay (days, median, IQR)		8 (4-17)
Deceased (mortality in %)		n=2368 (37%)

*Including intermediate care units / respiratory care units (IMCU / RCU). IQR = interquartile range; ICU = intensive care unit; HIV = human immunodeficiency virus; AIDS = Acquired immunodeficiency syndrome; NYHA = New York Heart Association; COPD = Chronic obstructive pulmonary disease; ECMO = extracorporeal membrane oxygenation;

Supplementary Table 2: Detailed clinical characteristics and outcome of transplanted COVID-19 ARDS patients (n=19).

	#1	#2	#3	#4	#5	#6	#7	#8	#9
Age	44	55	54	57	61	54	49	64	56
Gender	female	Male	Male	Male	Male	Male	Male	Male	Male
Length of MV until LTx (days)	52	29	55	57	50	39	41	28	30
Length of ECMO support until LTx (days)	45	23	47	46	43	27	41	17	2
History of septic episodes on ICU	No	No	No	No	No	No	No	No	No
CT findings	bilateral consolidations, signs of lung necrosis	bilateral consolidations, bilateral pneumothoraces, left sided pleural effusion, right-sided traction bronchiectasis	bilateral consolidations, signs of pulmonary embolism, bilateral pleural effusion	bilateral consolidations with pleural effusions	bilateral consolidations, left-sided pleural effusion, right-sided hemorrhage	bilateral pleural effusions, traction bronchiectasis	bilateral consolidations with pleural effusion	bilateral consolidations, multiple aerobronchogramm and pleural effusions	bilateral consolidations with aerobronchogramm and signs of fibrotic remodeling
Pneumothorax requiring chest tube insertion	No	Yes	No	Yes	No	No	No	No	No
Pulmonary haemorrhage	Yes	Yes	No	Yes	Yes	No	No	No	no
Lung compliance at time of listing (mL/cm H_20)	2.6	9.7	8.3	7.5	6.8	11.1	N/A	0.8	12.4
Reason for failure of native lung recovery	Bilateral large necrotic areas in the parenchyma, nearly complete absence of alveolar ventilation, no clinical improvement despite >6 weeks ECMO support + >7 weeks MV	Recurrent pneumo,- and hemothoraces	Severe pulmonary embolism in combination with multiresistent antimicrobial colonization and no clinical improvement despite >6 weeks ECMO support + >7 weeks MV	Recurrent pneumo,- and hemothoraces, no clinical improvement despite >6 weeks ECMO support + >8 weeks MV	Recurrent hemothoraces, no clinical improvement despite >6 weeks ECMO support + >7 weeks MV	Increasing circulatory and respiratory instability, no clinical improvement despite >3 weeks ECMO support and >5 weeks MV	No clinical and radiological improvement despite >5 weeks ECMO support + MV, continuously increasing pulmonary arterial pressures during ICU stay and evidence of encapsulated pleural effusions	nearly complete absence of alveolar ventilation, increasing hemodynamic instability while fully dependent on ECMO support, fully consolidated lungs with evidence of encapsulated pleural effusions in chest CT	Severe bilateral consolidations and evidence of irreversible fibrotic changes affecting all lobes
Maximum AKI stage during ICU stay	no AKI	3	no AKI	3	no AKI	no AKI	no AKI	no AKI	no AKI
AKI stage at time of listing	no AKI	3	no AKI	3	no AKI	no AKI	no AKI	no AKI	no AKI
Type of LTx	Bilateral, no size reduction	Bilateral, no size reduction	Trilobar (right upper + right lower + left upper lobe)	Bilateral, size-reduced (without middle lobe + lingula)	Bilateral, size-reduced (without middle lobe + lingula)	Bilateral, no size reduction	Bilateral, no size reduction	Bilateral, no size reduction	Bilateral, no size reduction
Postop ECMO prolongation	Yes	no	Yes	No	No	No	No	Yes	No
Time until able to dangle at bedside (days)	24	8	19	18	Not reached	12	5	5	6
Time until able to stand with help (days)	36	25	96	49	Not reached	23	7	20	22
Length of ICU stay	63	55	98	80	Not reached	37	12	32	27
Length of overall hospital stay	108	68	134	Not reached	Not reached	68	54	40	57
Major postoperative complications	hemothorax → revision, CIP, candida encephalitis	CIP, temporary atrial fibrillation, secondary sclerosing cholangitis	reperfusion edema, wound infection, coagulation dysfunction, temporary hemofiltration, CIP, subdural hematoma	CIP, hemothorax → revision, renal replacement therapy, secondary sclerosing cholangitis	CIP, secondary sclerosing cholangitis	CIP, wound infection, temporary renal replacement therapy	CIP, thrombosis of the subclavian and ulnar artery, gastrointestinal hemorrhage	CIP, hemothorax → revision, renal replacement therapy, secondary sclerosing cholangitis	CIP, phrenic nerve lesion palsy → diaphragm plication
Discharged from hospital	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Follow up (days)	450	300	147	154	66	207	189	180	162
Alive / dead (cause of death)	alive	alive	dead (subdural hematoma)	dead (liver failure)	dead (liver failure)	alive	alive	alive	alive

MV= mechanical ventilation; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; CT = computed tomography; AKI = acute kidney injury; N/A = not applicable; CIP = critical illness polyneuropathy;

	#10	#11	#12	#13	#14	#15	#16	#17	#18	#19
Age	46	64	58	34	61	56	53	47	62	57
Gender	Female	Male	Male	Female	Male	Male	Male	Male	Male	Male
Length of MV until LTx (days)	52	60	50	46	51	38	76	38	47	82
Length of ECMO support until LTx	52	23	8	45	43	29	66	36	34	59
History of septic episodes on ICU	Yes	No	Yes	No	Yes	No	No	Yes	Yes	No
CT findings	bilateral consolidations with pneumo-thoraces	bilateral consolidations with signs of fibrotic remodeling affecting all lobes	bilateral consolidations with traction bronchiectasis and pleural effusions	bilateral consolidations with distinct areobroncho-gramm and pleural effusion	bilateral consolidations with pleural effusions, aerobroncho-gramm, traction bronchiectasis	bilateral consoli-dations, traction bronchi-ectasis, bilareral pleural effusions	bilateral consolidations with aerobroncho-gramm	bilateral consolidations, right-sided pneumothorax	bilateral consolidations with pneumo-thoraces, in situ thrombosis	bilateral consolidations with aerobroncho-gramm and pleural effusions, traction bronchiectasis
Pneumothorax requiring chest tube insertion	yes	no	no	No	No	No	Yes	Yes	No	No
Pulmonary haemorrhage	No	no	No	no	No	No	Yes	No	No	no
Lung compliance at time of listing (mL/cm H_20)	6.0	7.9	33.3	4.8	12.6	5.3	N/A	27.9	13.7	8.8
Reason for failure of native lung recovery	Recurrent pneumothoraces, no clinical improvement despite >7 weeks ECMO support + MV	Severe bilateral consolidations and evidence of irreversible fibrotic changes of the lungs, no clinical improvement despite >3 weeks ECMO support and >8 weeks MV	Evidence of severe traction bronchiectasis in combination with encapsulated pleural effusions, prolonged MV >7 weeks + no respiratory improvement on ECMO support	no clinical improvement despite >6 weeks ECMO support + MV	no clinical improvement despite >6 weeks ECMO support + MV	no clinical improvement despite >4 weeks ECMO support + >5 weeks MV	Recurrent pneumo,- and hemothoraces, no clinical improvement despite >9 weeks ECMO support + >10 weeks MV	Recurrent pneumothoraces, no clinical improvement despite >5 weeks ECMO support + MV	no clinical improvement despite >4 weeks ECMO support + >6 weeks MV	no clinical improvement despite >8 weeks ECMO support + >11 weeks MV
Maximum AKI stage during ICU stay	no AKI	3	no AKI	no AKI	no AKI	no AKI	no AKI	no AKI	no AKI	3
AKI stage at time of listing	no AKI	3	no AKI	no AKI	no AKI	no AKI	no AKI	no AKI	no AKI	3
Type of LTx	Bilateral, no size reduction	Bilateral, no size reduction	Bilateral, no size reduction	Bilateral, size-reduced (without middle lobe + lingula)	Bilateral, size-reduced (without middle lobe + lingula)	Bilateral, no size reduction	Bilateral, no size reduction	Bilateral, no size reduction	Bilateral, size-reduced (without middle lobe + lingula)	Bilateral, no size reduction
Postop ECMO prolongation	Yes	No	No	No	Yes	No	Yes	No	No	No
Time until able to dangle at bedside (days)	13	12	7	10	6	8	44	11	10	14
Time until able to stand with help (days)	Not reached	55	20	20	26	16	Not reached	Not reached	15	Not reached
Length of ICU stay	90	Not reached	25	25	27	37	Still admitted	34	30	Still admitted
Length of overall hospital stay	Not reached	Not reached	49	64	Still admitted	50	Still admitted	Not reached	70	Still admitted
Major postoperative complications	CIP, intermittant atrial fibrillation, multiple venous thrombosis, secundary sclerosing cholangitis	CIP, renal insufficiency with replacement therapy required, bacterial pneumonia, secondary sclerosing cholangitis	CIP, jugular vein thrombosis, secondary sclerosing cholangitis, SIADH	CIP, posterior reversible encephalopathy syndrom, secondary sclerosing cholangitis	Pneumothorax → drainage, renal insufficiency, secundary sclerosing cholangitis	right side hemothorax → revision, CIP, temporary renal failure	hemothorax → revision, choledocho-lithiasis with repeat endoscopic intervention, esophageal perforation, CIP	CIP, secondary sclerosing cholangitis, temporary renal replacement therapy	CIP, abdominal hematoma, wound infection	hematothorax → multiple revisions, wound infection
Discharged from hospital	No	no	Yes	yes	no	yes	No	No	No	no
Follow up (days)	154	111	133	115	105	93	85	65	69	47
Alive / dead (cause of death)	alive	dead (multi-organ failure)	alive	alive	alive	alive	alive	dead (liver failure)	alive	alive

MV= mechanical ventilation; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; CT = computed tomography; N/A = not applicable; AKI = akute kidney injury; CIP = critical illness polyneuropathy; SIADH = syndrome of inappropriate antidiuretic hormone secretion