Early outcomes after lung transplantation for severe COVID-19: a series of the first consecutive cases from four countries

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Summary

Background Lung transplantation is a life-saving treatment for patients with end-stage lung disease; however, it is infrequently considered for patients with acute respiratory distress syndrome (ARDS) attributable to infectious causes. We aimed to describe the course of disease and early post-transplantation outcomes in critically ill patients with COVID-19 who failed to show lung recovery despite optimal medical management and were deemed to be at imminent risk of dying due to pulmonary complications.

Methods We established a multi-institutional case series that included the first consecutive transplants for severe COVID-19-associated ARDS known to us in the USA, Italy, Austria, and India. De-identified data from participating centres—including information relating to patient demographics and pre-COVID-19 characteristics, pretransplantation disease course, perioperative challenges, pathology of explanted lungs, and post-transplantation outcomes—were collected by Northwestern University (Chicago, IL, USA) and analysed.

Findings Between May 1 and Sept 30, 2020, 12 patients with COVID-19-associated ARDS underwent bilateral lung transplantation at six high-volume transplant centres in the USA (eight recipients at three centres), Italy (two recipients at one centre), Austria (one recipient), and India (one recipient). The median age of recipients was 48 years (IQR 41–51); three of the 12 patients were female. Chest imaging before transplantation showed severe lung damage that did not improve despite prolonged mechanical ventilation and extracorporeal membrane oxygenation. The lung transplant procedure was technically challenging, with severe pleural adhesions, hilar lymphadenopathy, and increased intraoperative transfusion requirements. Pathology of the explanted lungs showed extensive, ongoing acute lung injury with features of lung fibrosis. There was no recurrence of SARS-CoV-2 in the allografts. All patients with COVID-19 could be weaned off extracorporeal support and showed short-term survival similar to that of transplant recipients without COVID-19.

Interpretation The findings from our report show that lung transplantation is the only option for survival in some patients with severe, unresolving COVID-19-associated ARDS, and that the procedure can be done successfully, with good early post-transplantation outcomes, in carefully selected patients.

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Introduction

Lung transplantation is used to treat a variety of end-stage lung diseases; however, patients with acute lung injury due to infectious causes are generally not considered for transplantation.[1] Although sporadic cases of lung transplantation for COVID-19-associated acute respiratory distress syndrome (ARDS) have been reported,[2–4] insufficient data are available to inform selection criteria for potential recipients, the optimal timing of transplantation, and outcomes after transplantation. Additionally, several unaddressed concerns limit the use of lung transplantation as a therapy for patients with severe ARDS secondary to COVID-19. For example, the SARS-CoV-2 or superinfecting pathogens associated with viral pneumonia in the native

lung might recur in the allograft. Severe inflammation of the pleura and pulmonary hilar structures resulting from SARS-CoV-2 infection might create technical barriers to the transplantation procedure, leading to increased ischaemic time, need for intraoperative blood transfusion, and post-transplantation graft dysfunction. The profound deconditioning associated with prolonged mechanical ventilation, sedation, and neuromuscular blockade might also impede post-transplantation recovery and worsen outcomes.

As of Dec 10, 2020, more than 70 million people were reported to have had COVID-19, with more than 1·5 million deaths and 20 million active cases globally. Although several organs can be affected by COVID-19,

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For more on the **COVID-19
pandemic** see https://www.
worldometers.info/coronavirus/

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Research in context

Evidence before this study
To determine the role of lung transplantation in patients with
severe unresolving COVID-19, we searched PubMed and
Google Scholar using the terms "COVID-19", "SARS-CoV-2",
"COVID", "Lung transplantation/transplant", "acute respiratory
distress syndrome/ARDS", "lung injury", "mortality", "ICU",
"frailty", "complications", "medical course", "predictors of
recovery", "outcomes", and "pulmonary" in different
combinations. Articles in all languages from database
inception to Jan 10, 2021, were considered. Our search revealed
only two case reports of lung transplantation for COVID-19
from single transplant centres, including one report of
pathological findings in tissues explanted from three patients
undergoing lung transplantation. This study of pathology
showed the development of irrecoverable lung damage and
pulmonary fibrosis in some patients with COVID-19-associated
acute respiratory distress syndrome (ARDS), suggesting a need
for lung transplantation. Finally, a report was found evaluating
lung transplantation for patients with ARDS due to other
causes. We found no reports that discussed the
pretransplantation profile of recipients or post-transplantation
outcomes in a cohort of patients with severe COVID-19.
As such, there was an unmet need for a clinical series to better
understand the feasibility and safety of lung transplantation
for severe COVID-19-associated ARDS.

Added value of this study
Details from four cases included in the current series—surgical
aspects of lung transplantation in one recipient and details of
pathology in explanted lungs from three patients—have been
published in two recent articles, but detailed clinical
information was not provided previously. Inclusion of these

cases was required to support our intention-to-treat
approach, studying consecutive transplants from the
participating centres to eliminate selection bias in the
determination of post-transplantation outcomes. We show
that in multiple centres across the globe, double-lung
transplantation can be done successfully in patients with
COVID-19-associated irreversible lung damage. We provide
evidence of the reproducibility of lung transplantation in
carefully selected patients with severe COVID-19 and we show,
for the first time, that short-term post-transplantation
outcomes can be achieved that are similar to those of
transplant recipients without COVID-19. On the basis of our
pooled experience, we have been able to address questions
relating to candidate selection and the timing of and approach
to lung transplantation, and we propose guidelines that could
be used by multidisciplinary teams considering double-lung
transplantation for patients with severe COVID-19.

Implications of all the available evidence
The evidence shows that lung transplantation is feasible in
patients with irreversible lung injury associated with
COVID-19 who are unweanable from mechanical ventilation
or extracorporeal membrane oxygenation. Our case series,
building on case reports from single centres, will inform
regulators and payers in places like the USA, where payment
for procedures has to be approved, about the suitability of
lung transplantation as a life-saving treatment in carefully
selected patients. Further studies are needed to identify
patients who are likely to progress to irreversible lung
damage and to establish long-term outcomes in patients
with severe COVID-19 who undergo lung transplantation.

the lungs are the primary site of disease. A significant
proportion of patients with SARS-CoV-2, ranging from
6% to 10%, can progress to ARDS and require
mechanical ventilation.[5,6] Furthermore, the mortality of
patients with COVID-19-associated ARDS requiring
mechanical ventilation can exceed 20–40%.[7,8] Given the
millions of active cases combined with the increase in
COVID-19 case numbers due to second waves of the
pandemic in many countries, the number of patients
who require prolonged mechanical ventilation and
extracorporeal support, and the cumulative number of
deaths from COVID-19-associated ARDS, are expected
to rise or remain high. Hence, it is important to
consider lung transplantation as a life-saving therapy
for patients with COVID-19-associated ARDS when
medical therapy fails.

To provide evidence to guide the use of lung
transplantation as a treatment for patients with
COVID-19-associated ARDS and irreversible lung injury,
we aimed to describe the pooled experience of double-
lung transplantation for COVID-19 at high-volume lung

transplantation centres that performed the first such
transplants in their respective countries. Here we report
the indications for lung transplantation in patients with
non-resolving COVID-19-associated ARDS, the
perioperative challenges, the pathology observed in
explanted lungs from patients with severe and prolonged
SARS-CoV-2 pneumonia, and early outcomes after
transplantation. In view of these data, we suggest criteria
that could be used when lung transplantation is being
considered for patients with severe COVID-19, and
developed as further evidence emerges.

A video abstract is available online.

Methods
Study cohort
Our goal was to include all initial transplants performed
around the globe in patients with COVID-19-associated
ARDS. Peer-to-peer communication, scientific literature,
and media outlets including national newspapers, and
national and international television channels were used
to gain information on centres that had undertaken the

first transplants in their respective countries. At the time of data collection, to the best of our knowledge, all centres that had performed lung transplants for COVID-19 were identified. The first, consecutive lung transplants for severe COVID-19-related ARDS at six international centres were included in the series: Northwestern Medicine Lung Transplant Program, Northwestern University (Chicago, IL, USA; four recipients), University of Florida Health (Gainesville, FL, USA; three recipients), University of Milan (Milan, Italy; two recipients), Lung Transplant Program of the Medical University of Vienna (Vienna, Austria; one recipient), Norton Thoracic Institute (Phoenix, AZ, USA; one recipient), and MGM Healthcare (Chennai, India; one recipient). We were unable to include transplants done in China and South Korea. No patients with COVID-19 who had undergone lung transplantation at these centres at the time of data collection were excluded from the analysis. De-identified data from all centres were collected and analysed by Northwestern University (Chicago, IL, USA). All patients underwent bilateral lung transplantation. Whole lungs were used in 11 recipients, whereas one patient required lobar transplantation due to severe contraction of the pleural cavity.

This multi-institutional study was approved by the institutional review board of Northwestern University (STU00213616). Requirement to obtain consent for the analysis of consecutive cases was waived by the institutional review board. The lung tissue obtained from a single, non-consecutive case for matrix imaging was collected and processed after obtaining patient consent as part of a Northwestern University institutional review board-approved study (STU00212120).

COVID-19 care and consideration for lung transplantation

Patients received treatment according to the local standard of care from a multidisciplinary COVID-19 care team that included surgeons, infectious disease physicians, pulmonary and critical care physicians, and cardiologists at the respective centres (table 1). Referral to the lung transplantation team was made when at least 4 weeks had elapsed since the onset of ARDS and there was no evidence of lung recovery as agreed by the multidisciplinary team. Not all patients with severe COVID-19 who were treated at the respective centres were referred to lung transplantation after 4 weeks. Common reasons that precluded lung transplantation evaluation included multiorgan failure, inability to assess mental status if the patient was unresponsive or not awake, secondary complications such as sepsis or stroke, and general contraindications relevant to lung transplantation. Each patient was then evaluated by the lung transplantation team and considered a candidate for transplantation if other programmatic criteria were met, according to the International Society for Heart and Lung Transplantation guidelines.[9] Although the patients in this series were frail at the time of transplantation, they had been healthy

before the onset of COVID-19-associated ARDS. Thus, frailty alone was not considered to be exclusive. Patients with multiorgan dysfunction were excluded from lung transplantation evaluation for COVID-19; multiple organ transplantation in patients with COVID-19 was outside the scope of this study. Details of the transplant management followed for patients in our series are provided in the appendix (pp 1–2). All transplantations in this series, except the one in India, were performed by thoracic surgeons whose clinical practices are dedicated to non-cardiac and lung transplant procedures.

Data collection

For the 12 cases in this series, we collated information relating to patient demographics and pre-COVID-19 characteristics, including comorbidities, pretransplant-ation profile (including clinical and radiological features, treatment and management, medical course, and indications for lung transplantation), perioperative challenges (including transfusion requirement and technical challenges), pathological assessment of the explanted lungs, and post-transplantation outcomes. Details of the lung donors were also recorded.

SHIELD tissue clearing

After data from the 12 cases in our series had been collected, we used SHIELD tissue-clearing technology to evaluate the lung framework matrix in explanted lung tissue from an additional (non-consecutive) patient with severe COVID-19 who underwent a successful double-lung transplantation on the Northwestern Medicine Lung Transplant Program after 130 days of extracorporeal membrane oxygenation (ECMO) support and non-resolution of lung injury, and cases of end-stage emphysema and α1-antitrypsin deficiency for comparison. Tissue was sectioned into 100 μm slices and fixed using a modified SHIELD fixation protocol, described previously.[10] The fixed tissue slices were treated with 1 mL SHIELD-Off solution (1:1:2 double-distilled H_2O:SHIELD buffer:SHIELD epoxy) and incubated at 4°C for about 5 h. The tissue was then transferred to a clean plate containing SHIELD-On solution (1:1 SHIELD-On buffer:SHIELD epoxy) and incubated for 2·4 h at room temperature. Slices were cleared and placed under LifeCanvas Passive Clearance Buffer at 37°C until the tissue became opaque. They were then washed overnight in phosphate-buffered saline with 1% Triton X-100 (PBST) and stained in a 1:10000 dilution of Hoechst 33342 in PBST overnight. Tissue slices were then index matched in LifeCanvas Easy Index solution. Imaging was done using a Nikon W1-Spinning Disk Confocal Microscope at 20× magnification and 3D images were developed using Fiji.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Patients with COVID-19-associated ARDS
Sex	
Female	3 (25%)
Male	9 (75%)
Age, years	48 (41–51)
Height, cm	170 (168–176)
Weight, kg	74·5 (71–80)
Body-mass index, kg/m²	25·9 (24·8–26·8)
Blood group	
A	4 (33%)
B	2 (17%)
O	5 (42%)
AB	1 (8%)
Time from COVID-19 diagnosis to ICU admission, days	7 (3–8)
Time from COVID-19 diagnosis to intubation, days	8 (6–9)
Antiviral medication	
Ritonavir	2 (17%)
Lopinavir	3 (25%)
Tocilizumab	5 (42%)
Remdesevir	9 (75%)
Steroids	8 (67%)
Convalescent plasma	3 (25%)
Immunoglobulins	1 (8%)
Hydroxychloroquine	5 (42%)
Azithromycin	1 (8%)
Status at the time of listing	
Tracheostomy	10 (83%)
Type of ventilation	
PCV	8 (67%)
CPAP	1 (8%)
Nasal cannula	2 (17%)
Trach masking	1 (8%)
Lung compliance, mL/mbar	10 (6·7–12·3)
ECLS	
VV ECMO (single dual-lumen cannula)	6 (50%)
VV ECMO (two cannulae)	5 (42%)
No ECLS	1 (8%)
Length of ECLS support at the time of listing, days	49 (38–80)
Awake ECLS bridging	10 (83%)
Number of patients recovered from AKI	6 (50%)
Number of patients recovered from sepsis	11 (92%)
Creatinine, mg/dL	0·50 (0·38–0·62)
BUN, mg/dL	19·5 (9·2–34·3)
ASAT, U/L	23·7 (16–29)
ALAT, U/L	17 (12–28)
INR	1·45 (1·3–1·7)
C-reactive protein, mg/L	26·5 (20·7–33·7)
Leukocytes, g/L	11·1 (7·7–17·2)
Procalcitonin, ng/mL	0·3 (0·2–0·6)
Evidence of pulmonary bacterial superinfection	10 (83%)
Evidence of fungal colonisation	4 (33%)
(Table 1 continues in next column)	

	Patients with COVID-19-associated ARDS
(Continued from previous column)	
Right ventricular dysfunction	11 (92%)
mPAP	56 (35–64·5)
Time from COVID-19 diagnosis to listing, days	69 (51–82)
LAS	85·7 (81–89)
Transplantation	
Time on the waiting list, days	6 (4–9)
Clamshell incision	12 (100%)
VA ECMO intraoperative support	12 (100%)
Type of transplantation	
Whole lungs	11 (92%)
Lobar	1 (8%)
Surgery time (skin to skin), min	504 (448–649)
Total ischaemic time, min	336 (307–460)
Number of intraoperative pRBC	8 (5–15)
Number of intraoperative FFP	4 (3–7)
Post-transplant period	
Induction therapy	9 (75%)
Postoperative prolonged ECMO	10 (83%)
PGD at 72 h	
PGD 0	2
PGD 1	1
PGD 2	2
PGD 3	0
PGD ungradable	7
Length of mechanical ventilation, days	16 (4–21)
Length of stay in ICU, days	20 (13–24)
Length of hospital stay, days	37 (27–42)
Number of patients still in hospital*	1 (8%)
Complications	
AKI/CVVH	4 (33%)
Bleeding requiring chest reopening	3 (25%)
Critical illness neuropathy	3 (25%)
Complicated pleural effusion	1 (8%)
Dysexecutive syndrome	2 (17%)
Overall survival	
Alive	11 (92%)
Dead	1 (8%)
Follow-up after transplantation, days	80 (57–119)
Karnofsky Performance Status	80 (55–85)
Need for supplemental oxygen at the time of discharge	
Yes	2/11 (18%)
No	9/11 (82%)

Data are n (%), median (IQR), n, or n/n (%), unless stated otherwise. AKI=acute kidney injury. ALAT=alanine aminotransferase. ARDS=acute respiratory distress syndrome. ASAT=aspartate aminotransferase. BUN=blood urea nitrogen. CPAP=continuous positive airway pressure. CVVH=continuous venovenous haemofiltration. ECLS=extracorporeal life support. ICU=intensive care unit. INR=international normalised ratio. LAS=lung allocation score. mPAP=mean pulmonary arterial pressure. PCV=pressure-controlled ventilation. PGD=primary graft dysfunction. VA ECMO=venoarterial extracorporeal membrane oxygenation. VV ECMO=venovenous extracorporeal membrane oxygenation. pRBC=packed red blood cells. FFP=fresh frozen plasma. *Patients in hospital as of Oct 25, 2020.

Table 1: **Demographics and characteristics of the study cohort**

	Age, years	Centre	Comor-bidities	Body-mass index, kg/m²	Time from MV initiation to LTx, days	Tracheostomy	Time on ECMO at time of LTx, days	Awake or mobilising during bridging	CT findings before LTx	Total ischaemic time, h	Time in ICU after LTx, days	Time in hospital after LTx, days	Follow-up, days	Alive or dead
Patient 1	44	A	Yes	26·5	52	Yes	45	No	Consolidations, large necrotic areas	506	63	108	160	Alive
Patient 2	18	B	No	21·6	71	No	55	Yes	Pneumatocele, GGO, crazy paving, PNX	815	24	42	160	Alive
Patient 3	28	C	Yes	31·8	40	Yes	34	Yes	Extensive airspace opacities	315	21	28	143	Alive
Patient 4	48	B	No	26·1	70	Yes	54	Yes	UIP-like pattern	626	61	61	61	Dead
Patient 5	62	C	Yes	23·5	69	Yes	69	Yes	Complete opacification of the lungs bilaterally	301	15	38	112	Alive
Patient 6	51	D	Yes	25·3	103	Yes	103	Yes	Coarsened interstitial markings, subpleural cysts bilateral PNX	307	10	14	93	Alive
Patient 7	48	E	No	27·7	39	Yes	32	Yes	Multifocal consolidations with patchy ground glass opacities	353	10	26	90	Alive
Patient 8	52	F	Yes	26·7	114	Yes	86*	Yes	Traction bronchiectasis, diffuse ground glass	260	4	11	70	Alive
Patient 9	43	C	Yes	20·7	88	Yes	86	Yes	NA	306	24	42	63	Alive
Patient 10	34	D	Yes	36·6	77	Yes	77	Yes	Cystic bronchiectasis and extensive lower bilateral airspace disease, bilateral PNX	445	21	37	46	Alive
Patient 11	66	C	Yes	25·8	39	No	39	Yes	Fibrosis, honeycombing	318	15	Still admitted	33	Alive
Patient 12	51	D	No	25·4	67	Yes	53	Yes	Bilateral fibrotic changes with traction bronchiectasis	396	19	28	32	Alive

ECMO=extracorporeal membrane oxygenation. GGO=ground glass opacities. ICU=intensive care unit. LTx=lung transplantation. MV=mechanical ventilation. NA=not applicable. PNX=pneumothorax. UIP=usual interstitial pneumonia. *Patient had two runs of extracorporeal membrane oxygenation but was decannulated on mechanical ventilation at the time of transplantation. Some details from four cases included in this series have previously been published.[10,11]

Table 2: **Characteristics of individual transplant recipients**

Results

Between May 1 and Sept 30, 2020, 12 patients with COVID-19-associated ARDS underwent lung transplantation at the six international centres. Collectively, these centres did 145 lung transplants for patients without COVID-19 during this period. Although there was no waiting-list mortality among patients with COVID-19, two patients without COVID-19 died awaiting lung transplantation at the centre in India. The median age of the patients with COVID-19 was 48 years (IQR 41–51), and three (25%) of the 12 patients were female. Most patients were blood types O (five patients; 42%) or A (four; 33%). Four (33%) patients had no known comorbidities; the remaining eight (67%) patients presented with medically controlled diseases such as hypertension, diabetes, and psoriatic arthritis. The median body-mass index for the cohort was 25·9 kg/m² (IQR 24·8–26·8). Other demographic details are provided in table 1 and clinical characteristics of individuals in table 2.

Patients had a median of 7 days (IQR 3–8) from diagnosis to intensive care unit (ICU) admission and 8 days (6–9) from diagnosis to intubation. COVID-19-specific medical therapies included convalescent plasma (received by three patients; 25%), remdesivir (nine; 75%), tocilizumab (five; 42%), lopinavir (three; 25%), and steroids (eight; 67%). The ARDSNet guidelines informed patient management.[12] At lung transplant listing, ten patients (83%) had a tracheostomy. All patients but one were supported with venovenous ECMO (six with a single dual-lumen cannula, and five with conventional two cannulae) for a median of 49 days (IQR 38–80). The remaining patient had had two previous venovenous ECMO runs, but was weaned off extracorporeal support and required only mechanical ventilation at the time of transplant listing. Lung compliance was severely impaired, with a median 10 mL/mbar (IQR 6·7–12·3). Of the 12 patients, ten (83%) were awake while on ECMO and had medical decision-making capacity, and 11 (92%) had previous episodes of sepsis. Nosocomial pneumonias from multidrug resistant *Pseudomonas aeruginosa*, *Serratia marcescens*, *Klebsiella pneumoniae*, and *Achromobacter* sp were found in ten patients (83%). Complications such as pneumothorax and haemothorax were universal, and all patients required tube thoracostomy. Chest CT was obtained for lung transplantation evaluation in 11 patients (92%). Findings included interstitial fibrosis, traction and cystic bronchiectasis, extensive parenchymal consolidation with necrosis, bullous destruction and, hydropneumothoraces (figure 1).

The severity of lung disease was reflected in the study cohort's high median lung allocation score (LAS) of 85·7 (IQR 81–89). In the patients transplanted within the USA and the European transplant region, the LAS was prospectively calculated and used for listing purposes. However, for the centres outside the USA,
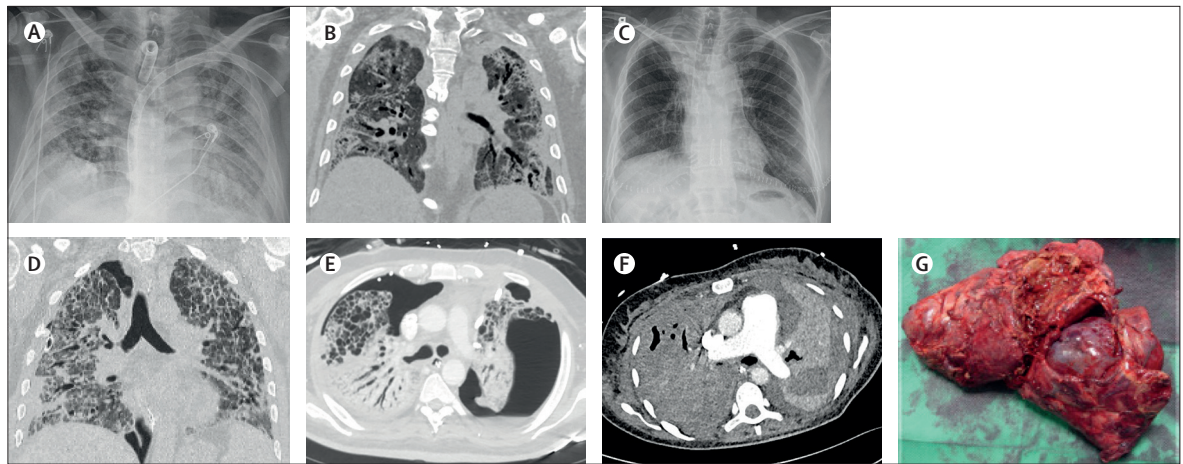
Figure 1: Imaging and gross pathology of transplant recipients
Typical chest radiograph (A) and CT (B) of a recipient undergoing lung transplantation for COVID-19-associated acute respiratory distress syndrome at the time of listing, showing honeycombing, consolidation, and bronchiectasis. (C) A chest radiograph of a representative recipient at the time of hospital discharge is given for comparison. (D–G) Typical radiological and gross pathological features seen in our patients at the time of listing: diffuse fibrosis in all lobes (D), pneumothoraces and shrinking lungs (E), parenchymal necrosis (F), and cavernous changes (G).
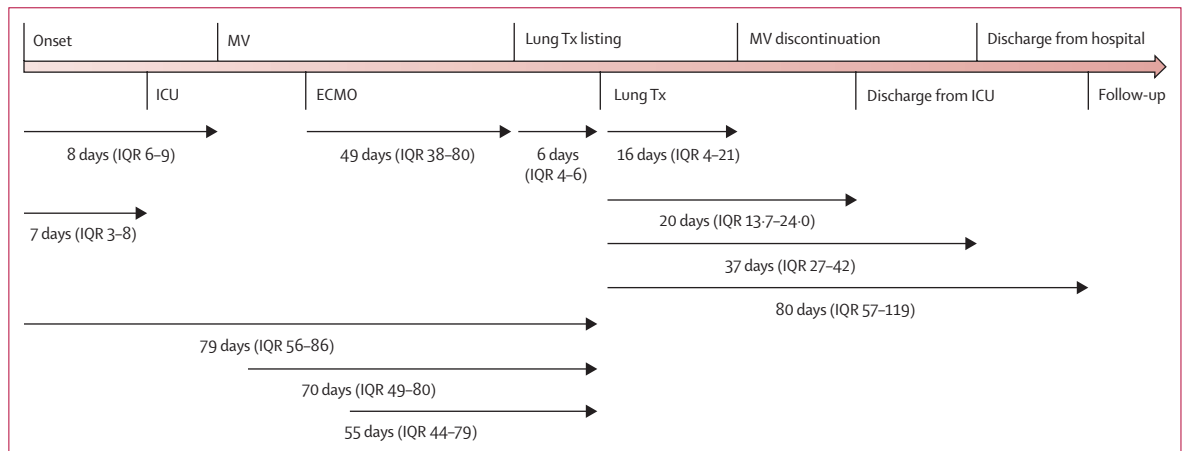

Figure 2: Timeline depicting different treatment phases throughout hospitalisation and follow-up
ICU=intensive care unit. MV=mechanical ventilation. ECMO=extracorporeal membrane oxygenation. Tx=transplantation.

the LAS was calculated retrospectively for the purposes of this analysis. Patients were transplanted a median of 70 days (IQR 49–80) after institution of mechanical ventilation and 55 days (44–79) after ECMO cannulation. The median wait time was 6 days (IQR 4–6; figure 2).

Details of the donors are provided in table 3. All were brain-death donors. The most frequent cause of death was traumatic brain injury and the median time from intubation of the donor to organ recovery was 84 h (IQR 66–104). All procedures were bilateral and done through a clamshell incision using central venoarterial ECMO support. Whereas whole-lung grafts were used in 11 patients, one patient required lobar transplantation due to severe contraction of the pleural cavity. Blood transfusion was required in all cases, with a median of 8 units of packed red blood cells (pRBCs; IQR 5–15) and 4 units of fresh frozen plasma (3–7).

Six cases (50%) needed more than 10 pRBCs intra-operatively, a requirement related to challenging dissection during native lung pneumonectomy. Dense pleuropulmonary adhesions were found in all cases, associated with highly vascularised and thickened mediastinal and parietal pleura. However, in patients without nosocomial infections or pleural interventions or empyema drainage, pleural adhesions were not as dense as compared with patients without nosocomial infections or pleural interventions. Bulky pulmonary hilar lymph-adenopathy was encountered in all cases, probably resulting from the acute inflammation and nosocomial infections. Given the high requirement for intraoperative blood transfusion, venovenous ECMO was empirically continued after transplantation in ten cases (83%) in anticipation of a high risk of primary graft dysfunction or allograft rejection.

In explanted lungs from all patients, diffuse alveolar damage was evident and consumed large areas of the lung parenchyma. With increasing time from onset of COVID-19 to transplantation (range 40–118 days), pulmonary fibrosis became more prominent. Other features included cavities with necrosis, areas of bronchopneumonia from secondary bacterial infection, acute interstitial pneumonitis including acute neutrophilic infiltrates within the interstitium and alveolar spaces, interstitial expansion by fibrosis, bronchiolisation of alveoli, and areas of microscopic honeycomb changes. In some patients, thrombi were also observed, with or without recanalisation, in small and intermediate vessels. Alveolar macrophages within the airspaces stained positive for iron, confirming the presence of alveolar haemorrhage consistent with earlier publications, including our 2020 reports.[10,11] Additionally, evaluation of explanted lung tissue from a COVID-19 lung transplant recipient using SHIELD tissue-clearing technology revealed architectural distortion similar to that observed in explanted lungs from patients undergoing lung transplantation for end-stage lung diseases such as emphysema and α1-antitrypsin deficiency (figure 3; video).

Mechanical ventilation was continued postoperatively for a median of 16 days (IQR 4–21). The 30-day survival was 100%, consistent with published outcomes for patients undergoing lung transplantation for non-COVID-19-related end-stage lung diseases (USA 30-day survival 97·7%). One patient in our series was recovering well but was still in hospital at postoperative day 33. For the remaining 11 patients, the median ICU stay was 20 days (IQR 13·7–24) and the median hospital stay was 37 days (27–42). Major post-transplantation morbidity included acute kidney failure requiring continuous renal replacement therapy in four patients (33%), haemothorax requiring reoperation in three (25%), and critical illness neuropathy in three (25%).[15] After a median follow-up of 80 days (range 32–160), 11 patients are alive and recovering well. Discontinuation of supplemental oxygen was possible in nine patients and the median post-transplantation Karnofsky Performance Status score was 80 (range 50–90). Unfortunately, one patient had critical illness neuropathy[15] and dysexecutive syndrome, and ultimately died due to *K pneumoniae* carbapenemase-producing *K pneumonia* sepsis on post-transplantation day 61.

Discussion

ARDS and pneumonia are allowable indications for lung transplantation according to the United Network for Organ Sharing (UNOS), which is contracted by the Health Resources and Services Administration of the US Department of Health and Human Services to administer the federal Organ Procurement and Transplant Network in the USA. However, although post-transplantation outcomes for chronic lung diseases are established, the

	Donors
Sex	
Female	4 (33%)
Male	8 (67%)
Age, years	34 (29–43)
Height, cm	173 (170–179)
Weight, kg	84 (76–92)
Predicted total lung capacity, L	6·1 (5·1–7·2)
Smoking history (current or past smoker)	5 (42%)
Cause of death	
Subarachnoid bleeding	1 (8%)
Traumatic brain injury	6 (50%)
Overdose	3 (25%)
Intracerebral bleeding	1 (8%)
Ischaemic brain Injury	1 (8%)
Chest x-ray	
Normal	7 (58%)
Abnormal	5 (42%)
Median intubation time, h	84 (66–105)
PaO$_2$/FiO$_2$ at time of offer	417 (362–489)
PaCO$_2$ at time of offer, mmHg	39 (35–45)
Bronchoscopy	
Normal	9 (75%)
Abnormal	3 (25%)
Type of donor[13]	
Ideal	3 (25%)
Marginal	9 (75%)
Median Oto score[14]	5 (3–7)

Data are n (%) or median (IQR). PaCO$_2$=partial pressure of arterial carbon dioxide. PaO$_2$/FiO$_2$=ratio of partial pressure of arterial oxygen to fraction of inspired oxygen.

Table 3: Donor characteristics

See **Online** for video

For the **Scientific Registry of Transplant Recipients** see https://www.srtr.org

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benefit of lung transplantation for patients with ARDS is unclear due to the dearth of reported experience.[16] Furthermore, patients with severe COVID-19 are critically ill and develop considerable ICU-related comorbidities by the time lung recovery is deemed unlikely and transplantation is considered. The course of severe COVID-19 is also often complicated by pulmonary complications such as pneumothorax, haemothorax, empyema, lung necrosis, and nosocomial pneumonias.[17] Hence, there are concerns related to the technical feasibility of lung transplantation in these patients, potentially inferior post-transplantation outcomes due to frailty, and recurrence of SARS-CoV-2 or nosocomial pathogens after transplantation. In view of these concerns, our study—based on an international cohort—provides evidence to support lung transplantation as a viable life-saving treatment option in selected patients with severe COVID-19-associated ARDS and irreversible lung injury. Consideration of lung transplantation in such patients is particularly important, because SARS-CoV-2 continues to infect hundreds of thousands of
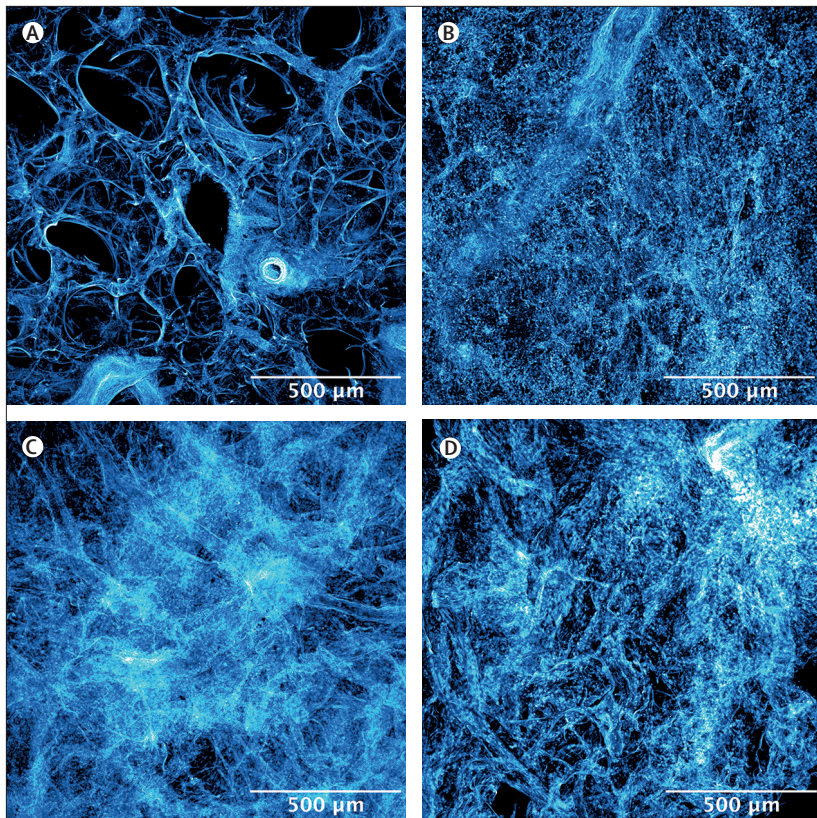
Figure 3: SHIELD tissue-cleared imaging of human lungs in late-stage severe COVID-19
Cleared lung tissue allowed visualisation of the collagen structure and matrix of the lung tissue (cyan; original magnification 10×). (A) Normal collagen matrix of human lungs. (B) Destroyed matrix with inflammatory cells in explanted lungs from a lung transplant recipient with late-stage severe COVID-19. (C) Explanted lungs from a lung transplant recipient with end-stage emphysema. (D) Explanted lungs from a lung transplant recipient with end-stage α1-antitrypsin deficiency.

which would be best treated with a bilateral transplantation. Second, lung transplantation should be considered only when sufficient time has elapsed since the onset of ARDS and lung recovery is deemed unlikely. Consideration of lung transplantation too early in the disease course could result in deviation of the care pathway away from spontaneous recovery, reducing its likelihood. Although the length of time needed to determine irreversibility is currently unclear, we suggest that at least 4–6 weeks be allowed after the onset of ARDS before considering lung transplantation, except when severe pulmonary complications such as severe pulmonary hypertension with concomitant right ventricular failure, refractory nosocomial pneumonias, or recurrent pneumothoraces develop that cannot be medically managed with or without ECMO. Transplantation should be deferred in patients who show signs of lung recovery, as suggested by improvement in lung compliance, chest radiographs, and gas exchange. Third, all attempts should be made to wean the sedation and awaken the patient so that they can participate in transplantation decision making. However, this process can take days to weeks in patients who have remained deeply sedated and received neuromuscular blockade. Furthermore, weaning of sedation can often be associated with the development of severe hypoxaemia and haemodynamic instability. Hence, for a small minority of patients in whom sedation wean cannot be accomplished, we suggest that consent to proceed with transplantation be made through a next-of-kin or a reliable medical power of attorney. Fourth, given that the duration of SARS-CoV-2 replication in the lungs of patients with severe disease is uncertain, we were concerned about ongoing infection at the time of transplantation and re-infection of the allograft. Accordingly, we did multiple bronchoscopic sampling of the lungs before transplantation and tested them for SARS-CoV-2 using PCR. Reassuringly, we did not detect viral transcripts or nosocomial pathogens after the transplantation. These observations are in agreement with studies suggesting that it is rare to detect replicating virus more than 10 days after infection with SARS-CoV-2,[18–20] although the PCR result can remain positive for several weeks beyond infectivity.[18] In cases where the PCR remains positive for extended durations, high cycle thresholds are seen (Ct >24) but infectivity is usually not evident.[18–20] Nonetheless, we suggest that two negative PCRs from bronchoalveolar fluid be obtained before listing. When medical urgency necessitates earlier consideration of transplantation, a viral culture can be obtained to ensure clearance of the pathogen. Fifth, deep sedation and neuromuscular blockade might be detrimental for post-transplantation outcomes.[21,22] Even 2–3 days after initiation of mechanical ventilation, the diaphragm can lose up to 50% of its fibres,[23] which can pose a substantial hindrance to post-transplantation recovery. Hence, sedation wean and participation in pretransplantation rehabilitation is highly encouraged.

people worldwide each day, a fraction of whom will progress to irreversible lung disease requiring prolonged mechanical ventilation, ECMO, or both. Without the possibility of lung transplantation, care would be typically withdrawn, leading to death—as would have been the case in each of the patients described in this Article, because there was no lung recovery despite prolonged extracorporeal support and optimised medical care.

We propose that patients considered for lung transplantation for severe COVID-19 should preferably be younger than 65 years, have no or manageable pre-existing comorbidities, and have lung injury from which they are unlikely to survive without lung transplantation—a decision made in a multidisciplinary manner. However, there are several considerations for lung transplantation pertaining to the eligibility of patients with COVID-19-associated ARDS. First, patients with COVID-19 have severely damaged lungs and might be susceptible to developing severe nosocomial pneumonia when they receive post-transplantation immunosuppression; thus, we propose that all patients undergo double-lung transplantation. Additionally, we found severe pulmonary hypertension in our recipients,

Panel: Proposed criteria for the selection of patients with severe COVID-19 for lung transplantation

General criteria
- Age younger than 65 years, extended to younger than 70 years in exceptionally fit individuals
- Single-organ failure; in selected cases, multiorgan transplantation can be considered
- No malignancy or disabling comorbidities
- No dependence (alcohol, drugs, other) and not an active smoker
- Body-mass index in the range of 17–32 kg/m², with exceptions on a case-by-case basis
- Postoperative social support available (at least one reliable primary and one secondary caregiver identified)
- Insurance approval obtained or financial support established for transplant-related care, as applicable
- Patient and caregivers agreeable to lung transplantation and willing to relocate close to the transplantation centre for a period established by the transplantation centre

Neurocognitive status
- Patient is awake and interactive, with exceptions in selected cases if sedation wean is associated with severe hypoxaemia and haemodynamic changes
- If not awake and interactive, evidence supporting the absence of irreversible brain injury is obtained through physical assessment and brain imaging or neuropsychological consultation; an individual with medical power of attorney is identified who can make informed decisions consistent with patient's goals and consent to transplantation

General condition
- Patient is participating in physical therapy while hospitalised; exceptions can be made in selected cases if transplant evaluation is urgent, the patient has a high potential for post-transplantation recovery, and rehabilitation is hindered mainly due to lung injury associated with severe COVID-19

COVID-19 status
- Two negative PCR tests of bronchoalveolar lavage fluid are obtained, 24 h apart; in such cases, transplantation can be considered regardless of nasopharyngeal swabs when at least 4 weeks have elapsed since COVID-19 symptom onset, although both might be requested in some patients with a pre-existing immunosuppressive state, owing to concerns of prolonged shedding of replication-competent virus
- If separated from the ventilator with no tracheostomy, two negative PCR tests of nasopharyngeal swabs are obtained, 24 h apart
- When available, viral cultures are negative, confirming the absence of replication-competent virus in the potential transplant recipient; bronchoalveolar lavage should be used, when possible

Evidence of irreversible lung damage
- At least 4 weeks have elapsed since the onset of severe acute respiratory distress syndrome; rarely, evaluation for lung transplantation can be considered earlier than 4 weeks if potentially lethal pulmonary complications develop that cannot be managed medically or through the use of extracorporeal membrane oxygenation
- Lung recovery is deemed unlikely by at least two physicians from two different specialties (surgery, critical care, or pulmonary medicine), despite optimised medical care; transplantation should not be considered if ongoing lung improvement is seen, regardless of the time elapsed

Finally, the role of multiorgan transplantation in patients with COVID-19 might be evaluated in the future. The authors have developed consensus criteria that can be used for the consideration of double-lung transplantation in patients with severe COVID-19 (panel). Additionally, participating centres have received numerous transfer calls for the consideration of lung transplantation for patients with COVID-19, and have developed procedures to screen such patients that are appropriate for their clinical practice. As an example, Northwestern University and Northwestern Memorial Hospital developed an intake form (appendix pp 4–5), which could serve as a template to be modified on the basis of practices and policies of programmes considering lung transplantation for patients with severe COVID-19. We have also found that video consultation can be helpful before the transfer of such patients.

The positive early post-transplantation outcomes in our cohort should not lead to underestimation of the medical complexity of these transplants or the need for substantial resources. Lung transplantation for COVID-19-related ARDS is associated with significantly increased bleeding. Prolonged ECMO leads to platelet dysfunction in a considerable proportion of patients as they are bridged to transplant.[24] Pleural adhesions and an overall fragile tissue quality further increase intraoperative bleeding, potentially increasing postoperative risk. Additionally, the patients in this cohort were frail before transplantation (table 1), which has been proposed as a possible contraindication to lung transplantation in patients with chronic end-stage lung disease.[9] Prolonged ventilation and difficult recovery are expected after transplantation because patients are generally deconditioned. However, the risk of severe complications and functional debilitation after ARDS has been shown to be associated with increasing age and the presence of comorbidities at baseline, rather than the severity of illness.[25] Therefore, given that patients in our study were in a normal state of health before the onset of COVID-19-associated ARDS, we hypothesised that frailty was reversible after lung transplantation. The incidence of critical illness neuropathy was also low in our series, and we attribute

this to the healthy baseline status of our recipients and careful patient selection. All these transplant recipients required longer ICU stays and intensive rehabilitation after discharge from the hospital, which is not always necessary in recipients undergoing lung transplantation for chronic lung diseases. These observations provide further support for the importance of considering patients who were relatively young and healthy before the onset of COVID-19 so that they can safely tolerate post-transplantation rehabilitation.

Patients in our cohort had severe disease requiring ECMO to maintain adequate oxygenation and had failed to recover. All patients had complications of SARS-CoV-2 infection resulting in prolonged supportive ICU care, including markedly reduced lung compliance, repeated episodes of ventilator-associated pneumonia with increasingly resistant nosocomial pathogens, pneumothoraces requiring repeated tube thoracostomy, and bleeding into the pleural space and airways. In addition, pathology from the explants showed extensive and severe lung damage, with the development of lung fibrosis. The clinical state of the patients and the pathological findings suggest that the damage to the lungs was irreversible and transplantation was the sole viable treatment option for survival. Use of SHIELD tissue-clearing technology[10] to evaluate explanted lung tissue from a patient who underwent a successful double-lung transplantation for severe COVID-19 showed extensive damage of the lung matrix framework, similar to that of other end-stage lung diseases requiring lung transplantation (figure 3; video). End-stage lung disease with destruction of matrix architecture might be driven by aberrant immune activation in the form of spatially localised, self-sustaining inflammatory circuits between SARS-CoV-2-infected alveolar macrophages and activated T cells that slowly progress to involve the entire lung.[26] The resulting loss of tissue architecture allows colonisation and then infection by increasingly resistant nosocomial bacteria and fungi, propagating a cycle of progressive and irreversible lung destruction. Several attempts have been made to find prognostic tools for severe COVID-19-associated ARDS.[27,28] In a recent transcriptomic analysis at the single-cell level, fibrotic signatures have been identified in the alveolar macrophages and epithelial cells that could be potentially used to predict irrecoverable lung damage.[10] Additionally, bronchoscopic assessment might have a role in prognosticating irreversible lung parenchymal damage.[2,29] However, until further validation of these markers occurs, irreversible lung injury can only be determined clinically and radiologically.

We believe that the decision to proceed with lung transplantation should be made by a multidisciplinary team. At our centres, we include pulmonary and infectious disease specialists, critical care physicians, and surgeons, among others, in decision making. 4–6 weeks after the onset of severe COVID-19-associated ARDS and mechanical ventilator or ECMO support, we found the following indicators to be helpful in medical decision making for lung transplantation consideration: development of medically unmanageable pulmonary complications; presence of lung necrosis with cavitation, especially if associated with sepsis; presence of significant pulmonary hypertension; lung compliance at less than 20 mL/cm H$_2$O; and evidence of diffuse pulmonary fibrosis. However, these should not be considered as absolute criteria because our understanding of lung recovery in severe COVID-19 is still evolving.

Our main goal was to report the feasibility and reproducibility of lung transplantation for patients with irrecoverable ARDS associated with COVID-19 at experienced transplant centres globally. Details from four cases included in the current series—surgical aspects of lung transplantation in one recipient and details of pathology in explanted lungs from three patients—have been published in two recent articles,[10,14] but detailed clinical information was not provided in these reports. Inclusion of these patients was necessary for an intention-to-treat approach and to eliminate bias resulting from the exclusion of cases that might have had poor outcomes due to the early learning curve at the start of the pandemic, allowing us to derive meaningful post-transplantation outcomes and generate consensus guidelines. We recognise that subsequent transplants have been done by other centres. Additionally, other countries might have done lung transplantations of which we are unaware. Unfortunately, because UNOS in the USA did not include a diagnosis code for patients with COVID-19 until recently, and the Eurotransplant registry in Europe still does not capture that diagnosis, we do not have information related to those transplants. As such, we are unable to provide outcomes after COVID-19 lung transplantation outside the centres participating in this study, and our remarkable post-transplantation outcomes might not reflect national or international experience.

In summary, lung transplantation has a therapeutic role for well selected patients with COVID-19-associated ARDS when care has been escalated to prolonged mechanical ventilation or ECMO. We recommend that consideration of lung transplantation be limited to patients requiring mechanical ventilation or ECMO despite several weeks of optimal medical care, with advanced disease severity, radiological signs of irreversibility, and a high risk of developing life-threatening complications. Additionally, there might be a subset of patients who develop chronic pulmonary fibrosis from severe COVID-19 that might be considered for lung transplantation. Further studies are needed to identify patients who are likely to progress to irreversible lung damage and might benefit from early lung transplantation. Biomarkers such as KRT17[10] have been suggested to be predictive of lung failure, but further studies are needed to identify and validate biomarkers that could be used to guide treatment. Long-term

outcomes of lung transplantation in patients with severe COVID-19 remain to be determined. We hope that national regulatory bodies such as UNOS and Eurotransplant will consider tracking patients closely and publishing national experience so that standardised guidelines can be developed.

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