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Lung Transplantation for End-Stage Respiratory Failure After Severe COVID-19: A Report of 2 Cases

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ABSTRACT

We report 2 cases of bilateral lung transplantation for nonresolving coronavirus disease 2019 associated respiratory failure. In the first patient, the severe acute respiratory syndrome coronavirus 2 infection caused acute respiratory distress syndrome requiring prolonged extracorporeal membrane oxygenation support; in the second patient, coronavirus disease 2019 resulted in irreversible pulmonary fibrosis requiring only ventilatory support. The 2 cases represent the 2 ends of the spectrum showing significant differences in preoperative and postoperative courses.

THE first European report of lung transplantation (LTx) for severe coronavirus disease 2019 (COVID-19)–associated acute respiratory distress syndrome (ARDS) by Lang et al [1] was quickly followed by reports from high-volume centers in the United States, Italy, and India [2,3]. To our knowledge, there have been 23 cases of LTx for COVID-19–related pulmonary disease reported in the literature so far [3–5]. Experiences are limited, and data on patient selection, postoperative care, and outcomes remain scarce.

CASE PRESENTATION

Case 1

In December 2020, a successful LTx was performed in a 34-year-old male patient with COVID-19–associated ARDS without significant comorbidities Fig. 1.

Mechanical ventilation was required for 11 days, followed by extracorporeal membrane oxygenation (ECMO) support for 27 days without any clinical or radiological improvement. The patient was then listed for LTx. The patient was deeply sedated using a maximum dose of sevoflurane, dexmedetomidine, midazolam, fentanyl, and neuromuscular blockers because every attempt to reduce sedation resulted in agitation and clinical deterioration. The patient was therefore unable to discuss treatment options and consent to LTx.

A size-reduced (without the middle lobe and lingula) donor lung of predicted total lung capacity (pTLC) of 7.7 L was transplanted to this patient with a pTLC of 7.3 L. ECMO was

successfully removed in the operating room, but because of ventilatory problems (low tidal volumes and elevated partial pressure of carbon dioxide) after approximation of the ribs, the definitive chest closure was delayed for 2 days.

The patient was weaned from mechanical ventilation on postoperative day (POD) 120, transferred to the medical ward on POD 138, and discharged home on POD 178 Fig. 2. During this long postoperative course, he also became severely depressed and received psychiatric evaluation and treatment.

Case 2

In February 2021, a second successful LTx was performed in a previously healthy 53-year-old man with respiratory failure for irreversible post-COVID-19 pulmonary fibrosis Fig. 3.

The patient was listed for LTx after 57 days of mechanical ventilation without any clinical and radiological improvement. In addition to pressure-controlled ventilation with high oxygen concentration, inhaled nitric oxygen was administered, but ECMO support was not needed. The patient did not require any sedation and was undergoing physiotherapy while being mechanically ventilated. He was also able to discuss treatment options and consent to LTx.

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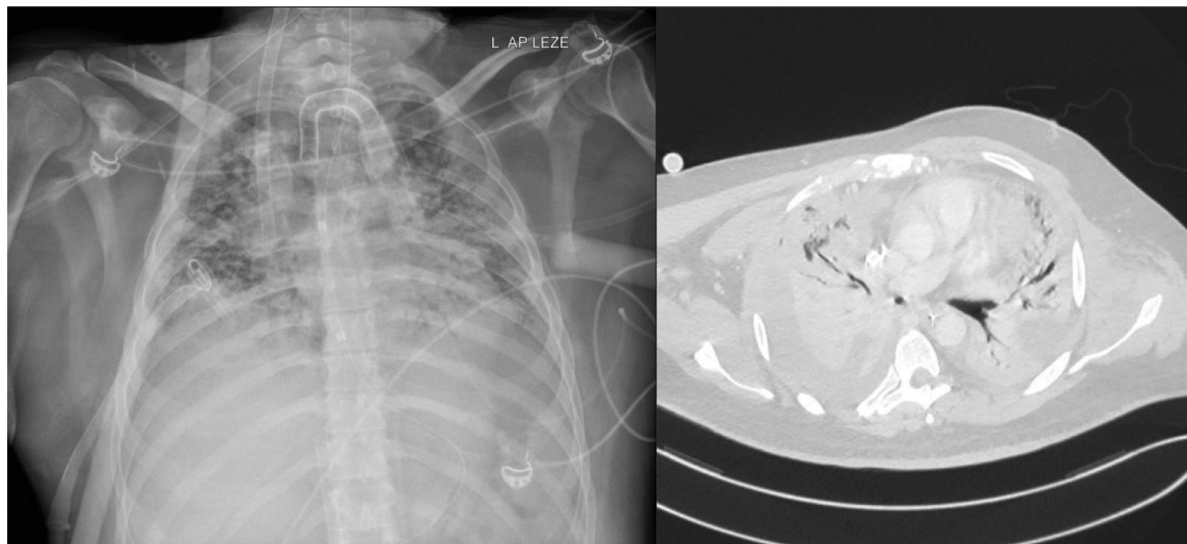


Fig 1. Patient 1 pretransplant chest x-ray and computed tomography.

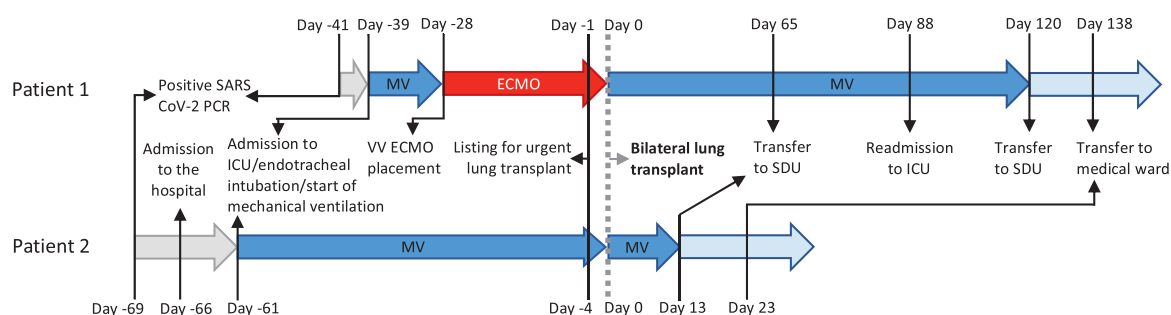


Fig 2. Timeline comparison for patient 1 and patient 2. ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MV, mechanical ventilation; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SDU, step-down unit; VV, veno-venous.

An entire right lung and a left upper lobe of a donor lung with pTLC of 7.3 L were transplanted to this patient with pTLC of 7.0 L. The patient was weaned from mechanical ventilation on POD 13, transferred to the medical ward on POD 23, and discharged home on POD 52 [Fig. 2](#).

DISCUSSION

Although both patients received LTx for severe respiratory failure after COVID-19 pneumonia, their conditions differed significantly, resulting in 2 completely different postoperative pathways.

1. The patient with COVID-19 with ARDS required deep sedation with ECMO support and later underwent LTx without first-person consent, resulting in an extremely prolonged hospital stay.
2. The patient with post-COVID-19 pulmonary fibrosis was, on the other hand, fully conscious and ambulatory, albeit mechanically ventilated, and recovered very rapidly after LTx.

Data on ECMO bridge to transplantation from large-volume centers show improved outcomes in awake patients who managed to undergo physiotherapy and become ambulatory [\[6\]](#). In our 2 cases, the pretransplant rehabilitation significantly improved outcomes and speeded up weaning from mechanical ventilation.

When facing the challenge of lung transplantation in patients with COVID-19, the selection criteria are critical and may require some adjustments to those proposed by Cypel and Keshavjee [\[7\]](#).

- Many patients with COVID-19–related ARDS require deep sedation to reduce oxygen consumption and breathing overdrive. Thus, discussing LTx with the patient may often be hindered [\[8,9\]](#) and was possibly the main factor to trigger depression in our first patient, which was only worsened by the loss of 2 family members because of COVID-19. Considering that depression and anxiety are risk factors for morbidity and mortality after organ transplantation [\[10\]](#), every step should be taken to ensure first-person consent and help the patient accept a life with a transplanted organ and lifelong

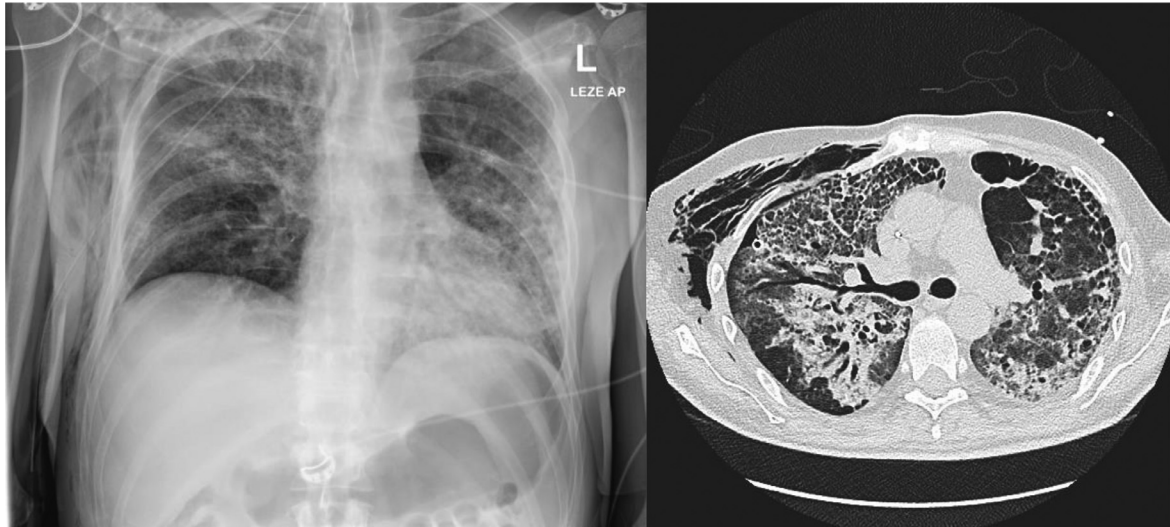


Fig 3. Patient 2 pretransplant chest x-ray and computed tomography.

immunosuppression. Nonetheless, as our experience indicates, when it comes to severe ARDS that require urgent life-saving lung transplantation, this may not always be possible.

- We also believe that the upper age limit should not exceed 55 years for several reasons. The median age of patients not recovering from ECMO support for COVID-19–related ARDS in a cohort of patients from Schmidt et al [8] was 52 years with an interquartile range of 48 to 58 years. Given the increased risk for a severe course of COVID-19 in the population aged over 55 years [11], the 55 to 65 age group may easily exceed the limited LTx capacity and incapacitate centers from transplanting younger and more promising candidates and patients with other indications. Moreover, recipient age is a predictor of postoperative mortality after ECMO bridging [12].

This work complied with the Declaration of Helsinki.

CONCLUSIONS

Lung transplantation should remain primarily a therapy for end-stage chronic pulmonary disease, although it could occasionally be used to treat ARDS. A broader international consensus should be sought to simplify decision making and avoid possible ethical concerns, especially during a pandemic.

REFERENCES

- [1] Lang C, Jaksch P, Hoda MA, Lang G, Staudinger T, Tschernko E, et al. Lung transplantation for COVID-19-associated acute respiratory distress syndrome in a PCR-positive patient. *Lancet Respir Med* 2020;8:1057–60.
- [2] Bharat A, Querrey M, Markov NS, Kim S, Kurihara C, Garza-Castillon R, et al. Lung transplantation for patients with severe COVID-19. *Sci Transl Med* 2020;12:eabe4282.
- [3] Bharat A, Machuca TN, Querrey M, Kurihara C, Garza-Castillon Jr R, Kim S, 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;9:487–97.
- [4] Hawkins RB, Mehaffey JH, Charles EJ, Mannem HC, Roeser M. Lung Transplantation for severe post–coronavirus disease 2019 respiratory failure. *Transplantation* 2021;105:1381–7.
- [5] CTV News. (2021 April 11). Doctors perform first double lung transplant on COVID-19 patient in Canada [press release]. <<https://www.ctvnews.ca/health/coronavirus/doctors-perform-first-double-lung-transplant-on-covid-19-patient-in-canada-1.5383468>>; 2021 [accessed 21.09.21].
- [6] Hoetzenecker K, Donahoe L, Yeung JC, Azad S, Fan E, Ferguson ND, et al. Extracorporeal life support as a bridge to lung transplantation—experience of a high-volume transplant center. *J Thorac Cardiovasc Surg* 2018;155:1316–28.e1.
- [7] Cypel M, Keshavjee S. When to consider lung transplantation for COVID-19. *Lancet Respir Med* 2020;8:944–6.
- [8] Schmidt M, Hajage D, Lebreton G, Monsel A, Voiriot G, Levy D, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med* 2020;8:1121–31.
- [9] Shang Y, Pan C, Yang X, Zhong M, Shang X, Wu Z, et al. Management of critically ill patients with COVID-19 in ICU: statement from front-line intensive care experts in Wuhan, China. *Ann Intens Care*. 2020;10:73.
- [10] Dew MA, Rosenberger EM, Myaskovsky L, DiMartini AF, DeVito Dabbs AJ, Posluszny DM, et al. Depression and anxiety as risk factors for morbidity and mortality after organ transplantation: a systematic review and meta-analysis. *Transplantation* 2015;100:988–1003.
- [11] Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med* 2020;180:1345–55.
- [12] Hayanga AJ, Aboagye J, Esper S, Shigemura N, Bermudez CA, D’Cunha J, et al. Extracorporeal membrane oxygenation as a bridge to lung transplantation in the United States: an evolving strategy in the management of rapidly advancing pulmonary disease. *J Thorac Cardiovasc Surg* 2015;149:291–6.