



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



# Post–COVID-19 Lung Transplantation Italian Pivotal Protocol: Some Ethical Considerations

C. Petrini<sup>a</sup>, D. Peritore<sup>b\*</sup>, L. Riva<sup>a</sup>, G. Florida<sup>a</sup>, S. Gainotti<sup>a</sup>, P.A. Grossi<sup>c</sup>, A.G. Castiglione<sup>d</sup>, M. Beretta<sup>e</sup>, F. Rea<sup>g</sup>, M. Nosotti<sup>f</sup>, L. Lombardini<sup>b</sup>, and M. Cardillo<sup>b</sup>

<sup>a</sup>Bioethics Unit, Italian National Institute of Health, Rome, Italy; <sup>b</sup>National Transplant Centre, Italian National Institute of Health, Rome, Italy; <sup>c</sup>Infectious and Tropical Diseases Unit, Department of Medicine and Surgery, University of Insubria, Varese, Italy; <sup>d</sup>Legal Medicine and Transplant Coordination, Policlinico San Martino Hospital, Genoa, Italy; <sup>e</sup>Department of Organ Failure and Transplantation, ASST Giovanni XXIII, Bergamo, Italy; <sup>f</sup>Department of Cardio-Thoracic-Vascular Sciences and Public Health, Unit of Thoracic Surgery and Lung Transplantation, Hospital University of Padua, Padua, Italy; and <sup>g</sup>Thoracic Surgery and Lung Transplantation Unit, University of Milan, Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

## ABSTRACT

SARS-CoV-2 mostly affects the respiratory system with clinical patterns ranging from the common cold to fatal pneumonia. During the first wave of the COVID-19 pandemic, owing to the high number of patients who were infected with SARS-CoV-2 and subsequently recovered, it has been shown that some patients with post–COVID-19 terminal respiratory failure need lung transplantation for survival. There is increasing evidence coming from worldwide observations that this procedure can be performed successfully in post–COVID-19 patients. However, owing to the scarcity of organs, there is a need to define the safety and efficacy of lung transplant for post–COVID-19 patients as compared to patients waiting for a lung transplant for other pre-existing conditions, in order to ensure that sound ethical criteria are applied in organ allocation. The Milan's Policlinic Lung Transplant Surgery Unit, with the revision of the National Second Opinion for Infectious Diseases and the contribution of the Italian Lung Transplant Centres and the Italian National Transplant Centre, set up a pivotal observational protocol for the lung transplant of patients infected and successively turned negative for SARS-CoV-2, albeit with lung consequences such as acute respiratory distress syndrome or some chronic interstitial lung disease.

The protocol was revised and approved by the Italian National Institute of Health Ethics Committee. Description of the protocol and some ethical considerations are reported in this article.

**C**ORONAVIRUSES are enveloped RNA viruses that cause respiratory diseases of varying severity, ranging from cold-like symptoms to fatal pneumonia. Death occurs most frequently as a consequence of acute respiratory distress syndrome (ARDS) or from subsequent pulmonary fibrosis.

As of early 2022, the new SARS-CoV-2 coronavirus pandemic has caused almost 5 hundred million infections and more than 6 million deaths worldwide [1]. In Italy, approximately 14.5 million infections and >159,000 COVID-19 related deaths were reported [2].

During the early months of the pandemic it was readily assumed that some patients, who had been suffering from COVID-19 lung infection and, subsequently, tested negative for the presence of the virus, might suffer post–COVID-19

terminal respiratory failure and require lung transplantation as a treatment.

However, transplantation for COVID-19-associated ARDS poses ethical dilemmas. Transplantation for irreversible lung disease is strongly characterized by a global shortage of donor organs; patients may die while on a waiting list and, consequently, recipients should be accurately selected [3].

Although in Italy patients with acute lung injury due to infections are generally not considered for transplantation, in 2020, there was already evidence that lung transplantation—the only

\*Address correspondence to Daniela Peritore, Istituto Superiore Di Sanità, via Gianio della Bella, n. 17 Roma, RM 00179, Italy  
E-mail: [daniela.peritore@iss.it](mailto:daniela.peritore@iss.it)

option for survival in some patients with severe unresolved COVID-19-associated ARDS—could be done successfully [4].

End-stage lung disease from COVID-19 is however a new entity: patients may benefit from transplant but there are limited data, especially on the long-term outcomes.

In order to monitor the outcomes of these transplants, the Milan's Policlinico Lung Transplant Surgery Unit, with the revision by the National Second Opinion for Infectious Diseases, and with the contribution of the Italian Lung Transplant Centres and the Italian National Transplant Centre, set-up an observational pilot protocol for lung transplantation in patients with ARDS or interstitial pulmonary fibrosis after the end of the COVID-19 infections. A fundamental assumption for the safety of the transplant is that the patient is negative for virus detection.

## MATERIALS AND METHODS

The aim of the Italian protocol is to evaluate the safety and efficacy of lung transplantation in patients with ARDS (group 1) and post-COVID-19 interstitial pulmonary fibrosis (group 2) on the basis of follow-up of treated patients. These 2 clinical settings represent the 2 different pathogenetic pictures of lung damage in patients affected by COVID-19: ARDS is characterized by a rapid progression of vascular endothelial damage that evolves in a few weeks into terminal respiratory failure; and fibrosis has a less rapid progression and is due to a progressive involvement of the pulmonary interstitium. From a clinical point of view, patients with ARDS require respiratory and/or mechanical assistance earlier than patients with respiratory failure derived from fibrosis [5]. Post-COVID-19 ARDS cases, with extracorporeal vascular support and/or invasive respiratory support, fall under the national emergency protocol while post-COVID-19 interstitial pulmonary fibrosis candidates fall under the transplant center allocation policy.

It may happen that a patient in serious clinical conditions, who does not meet all the requirements for access to the emergency program, urgently needs a transplant. In this case requests must be approved by the board for exceptions to the national protocol for pulmonary emergencies and the second national opinion for infectious diseases; if patients require invasive ventilatory assistance or extracorporeal vascular support because of their severe fibrosis, even after the acute phase, they will be managed according to the national emergency lung protocol.

Transplantation outcomes are compared with a third arm (control group) consisting of patients with ARDS or fibrosis not secondary to SARS-CoV-2 infection, and submitted to either elective or emergency lung transplantation.

Regardless of the clinical picture of COVID-19 lung injury, according to the indication in force in 2020, the absence of an active pre-transplant infection should be documented by polymerase chain reaction negativity for SARS-CoV-2 in 2 bronchoalveolar lavage specimens collected at least 24 hours apart. If the patient is not being intubated, a nasopharyngeal swab is sufficient. Monitoring is aimed primarily at documenting or excluding any recurrence of SARS-CoV-2 infection; assessment of perioperative mortality; and lung transplant-specific follow-up (ie, at the moment of discharge at 1, 3, 6 months, and 1 year). The probability of transplant success and the risks associated with the procedure and complications overlap with those of standard transplantation.

Patients have to sign an informed consent for enrollment and have to be referred to the National Transplant Centre, with a brief case report

**Table 1. Recipients Characteristics**

Mean age (y)	38.25
Sex: M/F	3/1
Blood group (%)	0 (50) A (25) B (25)

F, female; M, male.

highlighting the presence of inclusion criteria and the absence of exclusion criteria. In September 2020, this protocol was approved by the Ethics Committee of the Istituto Superiore di Sanità (Italian National Institute of Health), Rome, Italy. <H1>Results

From April 2020 to September 2021, the Italian National Transplant Centre received 4 lung transplant requests for recipients who had recovered from COVID-19 and met the enrollment criteria of the urgent lung transplant program (4 patients on extracorporeal membrane oxygenation): 2 patients with ARDS and 2 patients with interstitial fibrosis. Demographic characteristics are shown in Table 1. Of these 4 patients, 3 underwent transplantation; 1 request was discontinued by the Transplant Centre after 6 days because of clinical improvement in the patient's ARDS. Of the patients who underwent transplantation, 2 had a favorable outcome, 1 died on postoperative day 62 from klebsiella pneumoniae carbapenemase multi-drug resistant sepsis unrelated to the underlying pathology. The mean waiting time to transplantation was 11.33 days. None of the transplanted patients presented with SARS-CoV2 reactivation respectively after 15 and 2 months of follow-up (Table 2).

## DISCUSSION

In Italy, organ transplantation is part of the so-called Essential Levels of Care, that is, performances and services that the National Health Service is required to provide to all citizens, making them available throughout the entire national territory.

Italian, foreign European Union and non-European Union patients, assisted by the Italian National Health Service and requiring organ transplantation, are registered on a waiting list after receiving a positive opinion from their regional transplant center on the basis of criteria established by the transplant center itself based on the international literature and its own expertise. These individuals can be put on the waiting list for dead donor transplants.

**Table 2. Urgent Patient Post-COVID**

		Total	ARDS	Fibrosis
Urgent requests	Total	4	2	2
	ECMO support	4	2	2
	Ventilated	0	0	0
Transplants		3	1	2
Drop out (clinic improvement)		1	1	
Mean waiting time to transplant (d)		11.33	18	0
Transplant outcome	Exitus	1	0	1
	Alive with graft functioning	2	1	1
Follow-up (mo)		8.5	15	2

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation.

Lung transplantation is an elective therapy for end-stage respiratory failure secondary to a number of severe chronic diseases, that is, cystic fibrosis, pulmonary emphysema, chronic obstructive pulmonary disease, bronchiectasis, pulmonary hypertension or other rare diseases. Waiting list mortality [6] is a serious problem and the ultimate goal for the entire transplant system is surely to provide end-stage lung failure patients with well-functioning donor organs at the right time.

The allocation of lungs and the choice of the recipient are debated issues at international level because of the scarcity of these organs. There is a need to identify the most suitable recipient in order to avoid a futile transplant [7,8].

The standard allocation of lungs in Italy is organized on a regional basis, that is, the lungs are used by the transplant center of the same region where the donor is registered. The transplant center owning the organ chooses the most suitable recipient on the basis of its own local policies according to various principles that consider group identity/compatibility, donor/recipient size match, and list seniority. Some transplant centers assign the organ to the recipient according to the lung allocation score (LAS), that is, an algorithm that, considering several clinical parameters, provides an estimate of patient severity and transplant success [9]. Even the Lombardy region, the only Italian region that has more than 1 transplant center, adopts LAS as a criterion for organ assignment [10].

Lungs that cannot be allocated in the donor region (because the transplant center is not present or because it does not have suitable recipients), are offered to neighboring regions according to a continuous strip model, thus giving priority to the geographic criterion that guarantees the containment of ischemia times [11].

The use of LAS in the choice of the most suitable recipient considers each patient in their individuality, since it also considers the probability of posttransplant survival, reducing the risk of losing organs by transplanting patients in too critical conditions, and allowing the identification of the most correct timing to receive the organ. Lung emergency patients, differing from liver patients presenting an acute liver failure, are the result of progression of an underlying pathology leading to terminal respiratory failure requiring intubation or extracorporeal membrane oxygenation. Therefore, LAS could reduce the number of patients arriving in the terminal phase as it is effective in identifying the most appropriate time to transplant while still on the regular list.

In Italy, since November 2010, a nationwide urgent lung transplantation program has been implemented and patients on a waiting list—dependent on mechanical ventilation and/or extracorporeal lung support—could be transplanted on an urgent basis [12,13]. The emergency waiting list is considered active for a maximum period of 14 days and gives the patient the right to access the transplant thanks to the first compatible organs that become available throughout Italy. Strict inclusion and exclusion criteria (ie, age <50 years old, body mass index (BMI) <30, absence of multiorgan failure) are adopted to minimize the cases of graft failure [14]. Nevertheless, ethical concerns arise when lungs are allocated on an urgent basis, because elective patients might suffer from a longer wait on the list [15].

Careful evaluation and strict selection of recipients are crucial to improve the clinical impact of the program.

The availability of transplantable organs always falls far short of the needs of people waiting for a transplant, which creates imbalances. In Italy, the allocation of lung on a regional basis must respond to the principles of fairness and transparency and has to be based on scientifically valid criteria that can be documented for all involved. Physicians selecting the recipient of a donated organ are making decisions about how a scarce public resource should be used. Such a decision should be determined by criteria based on need, effectiveness and fairness publicly stated and publicly defended [16].

Organ transplantation is constantly facing new therapeutic indications; in some new circumstances it is impossible to be certain a priori that transplantation will give the same results as in established indications, but this possibility could not be excluded if the theory strongly supports it. The best ethical approach in these cases seems to be to carefully select recipients (so as not to divert resources from patients with established indications), to frame them within standardized protocols in order to define as soon as possible whether patients, with the new indication, should be fairly treated like all others in accessing transplantation.

The different phases of the COVID-19 pandemic have required adjustments in transplantation treatment strategies [17]. Globally, depending on the specificity of individual regions, programs have had to adjust risk-benefit calculations in the effort to apply principles of distributive justice by focusing on maximizing benefits often under conditions of worsening resource constraints. Treating people according to a principle of justice means treating people with the same need for a scarce resource equally [18].

According to our experience, the post-COVID-19 lung transplant protocol does not negatively affect patients already on the waiting list by allowing only the inclusion of a new therapeutic condition for which the available data have already proven favorable.

## CONCLUSIONS

At the beginning of the COVID-19 pandemic, the number of patients affected by the virus progressing to severe and catastrophic lung damage, despite the best available medical treatment, began to increase worldwide. Transplantologists have started to explore the possibility of lung transplantation as a life-saving intervention and a large number of transplants have been performed with encouraging results. Italy has developed a specific observational protocol for post-COVID-19 lung transplantation, defining inclusion and exclusion criteria and an adequate monitoring system to assess the safety and effectiveness of the procedure. Most candidates with post-COVID-19 terminal respiratory failure fall into the national lung emergency protocol. The probability of success of such a transplant, as well as the risks associated with the procedure and complications, are completely overlapping with those of standard transplantation. Lung transplantation is a resource-intensive treatment and, especially in post-COVID situations, the overall assessment by

government health care agencies and transplant providers is crucial, along with the decision-making and consent process with the patient [19]. The Italian protocol has received a favorable opinion by the Italian National Institute of Health Ethics Committee and as a national experience could contribute to the development of internationally standardized guidelines. In general, when approaching the issue of new indications, the Italian transplant network aims to carefully select new cases in order to define, as soon as possible, whether patients with the new indication have the right to be treated like all others in accessing transplantation.

## REFERENCES

- [1] World Health Organization. WHO Health Emergency Dashboard, <https://extranet.who.int/publicemergency>; 2022 [accessed 13.07.22]
- [2] European Center for Disease Prevention and Control. Covid-19 Situation Dashboard, <https://qap.ecdc.europa.eu/public/extensions/COVID-19/COVID-19.html#eu-eea-daily-tab>; 2022 [accessed 13.07.2022].
- [3] Lepper PM, Langer F, Wilkens H, et al. Lung transplantation for COVID-19-associated ARDS. *Lancet Respir Med* 2021;9:e88.
- [4] Bharat A, Machuca TN, Querrey M, et al. Early outcomes after lung transplantation for severe COVID-19: a series of the first consecutive cases from four countries. *Lancet Respir Med* 2021;9:487–97.
- [5] Merdji H, Mayeur S, Schenck M, et al. Histopathological features in fatal COVID-19 acute respiratory distress syndrome. *Med Intensiva (Engl Ed)* 2021;45:261–70.
- [6] Rate of 7.5% in 2020, data from the National Transplant Center, [https://www.trapianti.salute.gov.it/imgs/C\\_17\\_cntPubblicazioni\\_415\\_allegato.pdf](https://www.trapianti.salute.gov.it/imgs/C_17_cntPubblicazioni_415_allegato.pdf); 2020 [accessed 13.07.2022].
- [7] Egan TM. How should lungs be allocated for transplant? *Semin Respir Crit Care Med* 2018;39:126–37.
- [8] Gottlieb J. Lung allocation. *J Thorac Dis* 2017;9:2670–4.
- [9] Rosso L, Palleschi A, Tosi D, et al. Lung allocation score: a single-center simulation. *Transplant Proc* 2016;48:391–4.
- [10] Palleschi A, Benazzi E, Rossi CF, et al. Lung allocation score system: first Italian experience. *Transplant Proc* 2019;51:190–3.
- [11] Peritore D, Rizzato L, Trapani S, et al. Optimizing the use of available lungs. *Transplant Proc* 2017;49:692–4.
- [12] Pretagostini R, Rizzato L, Ricci A, et al. Urgent liver, heart, and lung transplantation programs in Italy: activities and evaluation of outcomes. *Transplant Proc* 2013;45:2616–8.
- [13] Pretagostini R, Peritore D, Rizzato L, et al. Urgent lung transplantation national program: the Italian experience. *Transplant Proc* 2013;45:2607–9.
- [14] National protocol for lung emergencies, [https://www.trapianti.salute.gov.it/imgs/C\\_17\\_cntPubblicazioni\\_119\\_allegato.pdf](https://www.trapianti.salute.gov.it/imgs/C_17_cntPubblicazioni_119_allegato.pdf).
- [15] Boffini M, Venuta F, Rea F, et al. Urgent lung transplant programme in Italy: analysis of the first 14 months. *Interact Cardiovasc Thorac Surg* 2014;19:795–800 discussion 800.
- [16] US department of Health and Human services. Rapporto della Task Force on Organ Transplantation. Issues and recommendations. Washington DC: US Dept. HHS; 1986. p. 86.
- [17] Stock PG, Wall A, Gardner J, et al. Ethical issues in the COVID era: doing the right thing depends on location, resources, and disease burden. *Transplantation* 2020;104:1316–20.
- [18] Wall AE, Pruett T, Stock P, Testa G. Coronavirus disease 2019: utilizing an ethical framework for rationing absolutely scarce health-care resources in transplant allocation decisions. *Am J Transplant* 2020;20:2332–6.
- [19] Walter K. Lung transplants for COVID-19—the option of last resort. *JAMA* 2021;326:14–6.