



Editorial

COVID-19: Impact on Lung Transplant Activity at a Large Brazilian Hospital

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The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in late 2019, and has caused a huge number of hospitalizations and deaths worldwide. Until now, there have been more than 500 million diagnosed cases and more than 6 million deaths, according to the Johns Hopkins coronavirus center [1]. Organ transplantation, like most other surgical procedures, and especially lung transplantation, has been extensively affected by the pandemic [2]. At our center, the Heart Institute of the Hospital das Clínicas in São Paulo, we experienced a unique situation brought on by the pandemic that resulted in the decline of lung transplant procedures in 2020 and 2021.

The Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo (HC-FMUSP, São Paulo, Brazil) is the largest hospital complex in Latin America, serving mainly the Brazilian public health service, the Unified Health System (SUS, Brasília, Brazil). This complex occupies an area of 600,000 m², with 2400 hospital beds spread throughout eight institutes: the Central Institute (ICHC, São Paulo, Brazil), the Psychiatry Institute (IPq, São Paulo, Brazil), the Orthopedics and Traumatology Institute (IOT, São Paulo, Brazil), the Medical Rehabilitation Institute (IMREA, São Paulo, Brazil), the Children's Institute (ICr, São Paulo, Brazil), the Heart Institute (InCor, São Paulo, Brazil), the Radiology Institute (InRad, São Paulo, Brazil) and the Cancer Institute (ICESP, São Paulo, Brazil) [3].

In times of normalcy, the ICHC houses most of the medical specialties of the HC-FMUSP complex. The department of thoracic surgery, and its subdivisions (including the lung transplant group), are housed at the Heart Institute (InCor, São Paulo, Brazil). However, the COVID-19 pandemic led to an extraordinary and historic mobilization, with the ICHC becoming a COVID-19 exclusive institute, and its several specialties temporarily relocated to the other institutes. Moreover, the clinical staff was divided into "COVID" and "non-COVID" sectors in order to reduce the intra-hospital spread of the disease. With these measures, the HC-FMUSP complex was able to increase the number of ICU beds in the ICHC from 83 to 300 and create 500 new infirmary beds³. Nonetheless, all non-urgent and non-cancer related hospitalization and surgical procedures were interrupted, including the lung transplant program.

This arrangement lasted from April to October 2020 and encompassed the first wave of COVID-19 that hit Brazil. During the final months of 2020 and the first semester of 2021 progress was slow, primarily due to the second and third waves. It was only in the second half of 2021, with mass vaccination, that the lung transplant program slowly began to recover.

As a result, between March 2020 and March 2022 (a two-year period) only 43 lung transplants were performed in our center. In the first year of the pandemic affecting Brazil (March 2020 to February 2021) only 14 transplants were performed by us and in the second year (April 2021 to March 2022) only 29 transplants were possible due to the COVID-19 impact on our health care system. This meant a significant decrease from the 39 transplants



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performed in 2019 alone [4]. Of those 43 procedures, four (9.3%) were done for patients with irreversible pulmonary fibrosis associated with COVID-19.

Patients with acute respiratory distress disorder (ARDS) do not usually need lung transplantation, so we reserve this treatment as a last resort for specific cases. Nevertheless, during this pandemic a series of cases were reported worldwide regarding chronic ARDS patients who received lung transplantations approximately four to six weeks after being diagnosed with COVID-19. These patients had shown no improvement in pulmonary function and all the other organs were functionally preserved. Following those reports, the Toronto Lung Transplant Group published in an editorial ten directives that should be considered before proposing lung transplantation as a therapy for respiratory failure due to advanced COVID-19 affecting the lungs [5]. In a nutshell the criteria included: 1. Age below 65; 2. No other organic dysfunction besides the lungs; 3. Allow enough time for recovery (typically four to six weeks); 4. Radiological evidence of irreversible lung damage; 5. Patients awake and conscious to understand the full scope of the proposed treatment; 6. Patients should be able to participate in physical rehabilitation; 7. Fulfill the regular requirements for a lung transplantation; 8. Negative PCR for SARS-CoV-2; 9. Be treated in a center with experience in high risk transplantation; 10. The center should have access to a broad donor pool and low waiting-list mortality.

Based on these directives from the Toronto Lung Transplant Group, the Technical Board of Thoracic Organs of the State of São Paulo presented its revised criteria for lung transplant in COVID-19 patients in April 2021 [6]: 1. Negative PCR for SARS-CoV-2 in lower respiratory tract sample; 2. Age below 65; 3. Irreversible lung damage after 6 weeks; 4. Body mass index (BMI) before hospital admission between 17 and 27; 5. Patients are hemodynamically stable; 6. Absence of active bacterial or fungal infection; 7. Patients awake and conscious to understand the full scope of the proposed treatment or being accompanied by guardians able to understand the situation and willing to be evaluated by nursing and psychology staff; 8. Green light for transplantation by social services staff and have no history of drug or tobacco use; 9. Able to participate in physical rehabilitation; 10. Transesophageal echocardiogram with no anomalies and ejection fraction greater than 50%; 11. Lack of coronary artery obstructions (with the exception of those which may be managed by catheter interventions); 12. No other organ dysfunction beside the lungs; 13. Provide full consent for the procedure to the lung transplant team; 14. Give the lung transplant team full autonomy to suspend the procedure in accordance with the evaluation of a multi-professional group.

From this point on, we received a series of cases both from inside and outside the HC-FMUSP complex for lung transplant evaluation. Cases from the HC-FMUSP complex were assessed in conjunction with the team responsible for the patient's care. Those from other hospitals were evaluated via telemedicine. If those patients fulfilled the requirements for lung transplantation, they would be transferred to the InCor for further evaluation. In addition to this, the processes of donor selection, organ procurement and operative tactics had to be adapted to the COVID-19 situation. The extended criteria were applied regarding recipient selection, as well as testing with PCR for SARS-CoV-2 and chest tomography. Only the organ procurement was done in the usual way, consisting of evaluation, perfusion and organ removal [6].

Furthermore, the lung transplant group took the lead in extracorporeal membrane oxygenation (ECMO) cannulation in COVID-19 patients. This was implemented initially for ventilatory disorders, but ultimately due to pulmonary hypertension associated with low lung compliance, as a bridge to recovery or even lung transplantation. Throughout this period, 24 COVID-19 patients were cannulated for venovenous ECMO. Of those, nine were successfully decannulated and four were subjected to lung transplantation.

During the surgical procedure in patients with irreversible pulmonary fibrosis associated with COVID-19, central venoarterial ECMO was implemented as intraoperative care, while maintaining peripheral venovenous ECMO at a low flow. The surgery was initiated on the side with a lower perfusion score and reperfusion of the lungs was done

slowly and gradually. The pressure of the pulmonary arteries was controlled by decreasing or increasing the circulatory assistance during the release of clamps from the pulmonary artery and left atrium. Throughout the transplantation, a cell saver was used and blood transfusion, replacement of fibrinogen and prothrombic factors had to be provided more often than in the pre-COVID-19 era. By the end of the transplant procedure, in the event of preserved biventricular function, the central venoarterial assistance would be removed and the ECMO circuit maintained by circulating a saline solution. If there was still a need for respiratory assistance after the transplant procedure, peripheral cannulation was maintained. Only one of the patients required this in the transplant period reported here. An extensive review of hemostasis parameters was performed and pleural drains were placed in both pleurae, in line with the usual practice, anteriorly and posteriorly [6,7].

Since COVID-19 patients subjected to lung transplantation had a long history of ICU stay and even previous use of ECMO, patients remained critically ill in the early post-operative days and were treated in the ICU. After transplantation we introduced the immunosuppressant therapy following our center's routine, and adjusted it with each patient's needs and acceptance. In addition to all the medications required for regular transplant recipients, early dialysis was often necessary, as well as additional antibiotics and antifungal medication for treatment of previous colonization or new infections. Tracheostomy proved to be an important tool as it allowed the patient to eat, walk and exercise [6]. We had a 100% survival rate for the 30th post-operative day, with the main complications being fungal infections in the early posttransplant phase.

Besides the impact the COVID-19 pandemic had on our surgical routine, it is also important to note its effects on the patients that are awaiting lung transplantation and those who already had received a lung transplant. Between March 2020 and March 2022, we reported 15 cases of COVID-19 in patients awaiting lung transplantation. Two of those patients died as a result of the infection or its complications, representing almost a 50% increase in our annual death rate of patients awaiting lung transplantation. Prior to COVID-19 we had about 4.5 deaths per year on the waiting list.

Moreover, as of March 2020, we had 213 post-lung transplant patients in follow-up, with a mean age of 46, being 51.8% male and 48.2% female. During this period, 29 (13.6%) patients were diagnosed with COVID-19. Of those, 23 patients were diagnosed, and received supervised treatment at our service and 6 had an external follow-up. Nine patients died (31.03%) as a result of this infection.

Lung transplantation in the midst of the pandemic proved to be a major challenge. Not only did we face the task of adapting our services to the most significant global health crisis since the 1918 Spanish Flu, but also regarding the search for viable donors and, most importantly, to prevent mortality among severely ill patients, who are either on the waiting list or have an acute disease that progressed to a chronic form of COVID-19 with respiratory failure.

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