EDITORIAL

Lung Transplant related to COVID-19 disease. *Auribus tenere lupum*. (Grab the wolf by the ears)

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Auribus tenere lupum (Grab the wolf by the ears). Publius Terentius calls upon the human will to overcome fear and confront seemingly unsurpassable situations. COVID-19 brought the whole of humanity to its knees, and with more than 1.5 million deaths in December 2020, we were faced with an enemy of invincible nature.

In June 2020, Barath performed the first lung transplant (LT) due to COVID-19 [1], situating the surgery in the map, as a part of treatment for the unrelenting pandemic. From this moment forward, as is historically common after a pioneering advancement, the diffusion of and debate over the procedure grew exponentially. Multiple centers began selecting patients to be rescued from respiratory disease due to COVID-19.

From August 2020 to September 2021, approximately 7% of transplants in the United States were performed on COVID-19 patients, with a 3-month survival very similar to that of transplant patients due to other etiologies [2].

Despite early success, there is not a current consensus and uncertainty surrounds the appropriateness of LT for COVID-19-related respiratory failure (ARDS and pulmonary fibrosis).

I congratulate the authors for their excellent review, where Freischlag analyzes the Organ Procurement and Transplant Network (OPTN) database in relation to LT due to COVID-19-related respiratory failure [3]. To my knowledge, this is the first report where a matched survival analysis between LT patients due to COVID-19-related respiratory failure and LT patients due to other etiologies has been established. The results are highly favorable and promising. It is worth to highlight the effort put forth to reach significant conclusions, given the considerable differences in baseline characteristics between recipients with COVID-19 (sample per se small) and the general population of LT recipients, even with the biases inherent to the nature of the study and considering that only 454 patients out of 37 000 non-COVID-19-related LTs were analyzed. This maintains the heterogeneity of the studied population and does not allow for conclusive results. Furthermore, there is a probability of selection bias and a lack of information about ECMO support.

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It is of particular interest to observe certain differences with Roach's previous review [4] on the UNOS database, which included only 214 LTs due to COVID-19-related respiratory failure between August 2020 and September 2021. Freischlag included 270 patients, which could be attributed to the period of study extending to December 2021. It must be noted that certain preoperative characteristics of LT recipients due to COVID-19 in both studies (Roach vs Freischlag) differ in some key aspects, such as the use of mechanical ventilation (53% vs 36.5%) and ECMO (64.5% vs 51.2%).

In the unmatched analysis, LT COVID-19 patients spent fewer days on the waitlist and had lower mortality rates during listing (4.1% vs 4.78%) than other transplants. Comparing this population to the one with other etiologies, the fact that transplants are performed faster probably relates to the patients' more critical and severe condition at the time of entering the waitlist. Evidently, their LAS is higher (73.80) which leads to receiving an allograft more quickly, thus lowering the mortality on the waitlist. Barath et al. reported similar results, although showing a higher mortality on the waitlist (18.9%) [5,6].

It is to be expected that authors report unfavorable short-term results for LT due to COVID-19. These patients had longer periods of intubation and postoperative ECMO, as well as higher rates of post-transplant dialysis. Nevertheless, there was no difference in the 30-day and 6-month in-hospital mortality rates between the two groups. Even when LT recipients due to COVID-19 were sicker than recipients with other etiologies (more ECMO, more ventilator and higher LAS), 30-day mortality was the same (2.2%) and survival at 90 days was higher than 95%. In short, the authors concluded that COVID-19 diagnosis at transplant was not associated with a greater risk of mortality.

Barath found 100% survival at 30 days, and 92% at 80 days [5]. In the preliminary analysis of the OPTN, Roach et al. also found a high survival in the COVID-19 cohort at 30 days and 6 months (97.7% and 94.4%) [4].

After the matched analysis, there are several conclusions that lead to important observations. Primarily, short-term results between COVID-19 patients and those with other etiologies are the same, with no statistically significant differences in in-hospital stay, ECMO and mechanical ventilation. Notably and quite controversially, the matched controls in this matched analysis had significantly higher 90-day mortality than COVID-19 transplants. Much is not yet understood about LT for COVID-19, although this result is intriguing since Chitaru et al. reported the same outcomes [5]. Thus, a deeper and more detailed analysis is needed. It is important to highlight that the favorable findings in mortality are the same for both analyses, which suggests that this surgical procedure is safe and effective in select patients. However, this statement may be met with a certain degree of controversy since surgical challenges due to the hostility of the thorax are highly complex and sizable.

Another important point of controversy surrounds the quality of life of these patients at the time of discharge. Freischlag found notably worse functional outcomes at discharge, which probably relates to the significant preoperative physical and nutritional deterioration. However, Chitaru et al. reported that the rate of improvement in the Karnofsky performance after lung transplant was 84.8% in the COVID-19 group vs 11% in the non-COVID-19 cohort [5], perhaps because of their relatively young age and healthy baseline medical condition prior to the onset of COVID-19 infection.

There is key information not specified in Freischlag's review which impacts the results significantly. Firstly, the type of preoperative ECMO utilized (VA,VV) and the cannulation strategy (peripheral, central, double lumen cannulas) are unknown. Secondly, a fundamental part of the use of ECMO as a bridge to transplant requires an ambulatory status, therefore it would be useful to know how many patients in ECMO as a bridge to transplant were a part of continuous physical rehabilitation. According to the authors and other reviews [1], LT for COVID-19 challenges this premise with the paradox of operating on patients with poor physical conditioning, a notable deviation from the regular guidelines for LT. Thirdly, there is no mention of data relating to mechanical circulatory support used during surgery (ECMO vs CPB). Lastly, the complications associated with preoperative ECMO are unknown, including right ventricular failure and the incidence of primary graft dysfunction (PGD).

In addition, another key piece of data not specified in Freischlag's review is the number or percentage of transplants performed due to acute respiratory distress syndrome vs. pulmonary fibrosis. Although both entities share the pathogenesis of COVID-19 infection, they each offer different complex challenges. The consequences of fibrothorax are impactful from preoperative selection, including facing severe size mismatch donor/recipient and influencing surgical strategies, since a fibrothorax with extensive deformity and loss of volume of the hemithorax represents one of the major challenges for LT.

The lack of current guidelines leads to certain variation in patient selection, which can bias the outcomes. Based on experience in the United States, LT recipients due to COVID-19 tend to be young, awake, able to participate in physical rehabilitation, have recent negative SARS-CoV-2 PCR result or infectivity assays using deep respiratory tract samples showing absence of viable virus, only single organ dysfunction, have lower BMIs, and show evidence of irreversible lung damage for more than 4-6 weeks, [1,6].

I congratulate the authors once again. Their results deserve recognition, showing excellent survival despite the severity of the disease. From my point of view, the factors that are decisively influential are adequate patient selection, improvement in postoperative critical care, and ECMO technology.

Operating on these patients demonstrates the essence of human nature itself. We are designed to confront adversity, and when on the verge of defeat, we find the strength to rise and start anew. *Fortuna iuvat audaces* (Fortune favours the brave).

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