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.

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Editorial

Lung transplantation in the COVID-19 Era: A multi-faceted challenge

Abbreviations

ARDS	acute respiratory distress syndrome
COVID-19	coronavirus disease 2019
ECMO	extra-corporeal membrane oxygenation
ICU	intensive care unit
IQR	interquartile range
LTx	lung transplantation
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOT	solid organ transplantation
WHO	World Health Organisation

As of 17 September 2021, COVID-19 had affected 226,844,344 individuals worldwide, of whom 4666,334 had died [1]. This massive pandemic has inflicted an unprecedented and onerous burden on hospitals everywhere. To protect the quality of care, preparations were made [2, 3], guidelines developed and implemented [4–6], and local strategies devised [7, 8].

Although physicians performing solid-organ transplantation (SOT) suspected that the COVID-19 pandemic would adversely affect both recipients and organ procurement [9–11], their fears fell far short of reality. French lung transplantation (LTx) units observed devastating effects [12] as soon as one month after the World Health Organisation classified COVID-19 as a pandemic [13].

Now, after more than 18 months fighting COVID-19, reports of direct consequences on SOT recipients and of collateral damage to transplant programs have been published. Among SOT patients, LTx recipients have been the most severely affected. In a somewhat ironic turn of events, LTx is now suggested to treat patients with severe SARS-CoV-2 pneumonia.

COVID-19 pneumonia in lung-transplant recipients

A British epidemiological study that used the analytics programme OpenSAFELY to assess the primary-care records of 17,278,392 adults found that having a transplanted organ was amongst the comorbid conditions associated with the greatest increase in COVID-19 severity, the adjusted hazard ratio for death being 3.53 (95%CI, 2.77–4.49) [14]. Among SOT recipients, those with transplanted lungs seem the most at risk. In a nationwide Spanish study of 778 SOT or haematopoietic-stem-cell recipients who contracted COVID-19 during the first 6 months of the pandemic, 54 patients had LTx, which was associated with a 46% mortality rate compared to 27% for the overall cohort (odds ratio, 2.5; 95%CI, 1.4–4.6) [15]. Another nationwide study, conducted in France, identified 35 LTx recipients with confirmed or strongly suspected COVID-19 during the first wave [16]. Mortality was lower, at 14.3%, and overweight was significantly associated with death in the multivariate analysis.

Collateral damage on lung transplantation (LTx) programmes

That the COVID-19 pandemic would have surreptitious effects was suspected very early on [12]. A study sought to determine whether the number of SOT procedures in France and the US was associated with the number of patients who had COVID-19 during the first few months of the pandemic [17]. The number of transplantations from decreased donors dropped massively, by 90.6% in France and 51.1% in the US, as the number of COVID-19 infections increased. The decrease occurred for all organs but was greatest for kidneys and, to a lesser extent, lungs.

Recent retrospective work has provided valuable insights into the consequences of the pandemic on SOT in 22 countries in Europe, the Americas, and Japan [18]. Data from national or regional organ-procurement and transplantation networks collected in 2019 and 2020 were compared. Raw data on numbers of transplantations of each organ were obtained and the number of patient life-years lost because of the drop in transplantation activity was estimated. The findings are of the utmost interest. First, the overall SOT decrease was 15.92%, with the drop being greatest for kidneys (19.14%) and smallest for hearts (5.44%). The 15.51% reduction in LTx masked substantial geographical differences, with a 66.67% increase in Slovenia (plus 6 LTx procedures in 2020 vs. 2019) and a 85.71% drop in Chile (minus 6 LTx procedures in 2020). In France, the drop was −31.27% (101 fewer LTx procedures in 2020). Second, an important original feature of the study is the estimation of the number of patient life-years lost due to the drop in SOT activity, based on a comparison of patients who received transplants to those who remained on the waiting list. For LTx candidates, the loss was 1799 years.

Data collected by the French biomedecine agency (Agence de la Biomédecine) indicate a decrease in access to organ transplants of candidates listed in 2020 compared to those listed during the two previous years. This decrease occurred for all organ types except hearts. LTx candidates saw their cumulative incidence of access to transplantation fall from 55 [interquartile range 52–59] in 2018 and 2019 to 45 [IQR 39–51] in 2020 ($p<0.01$). This major drop was not associated with significant changes in early post-LTx outcomes or in the 3-month post-listing cumulative incidence of death or delisting. Nevertheless, whether 3 months is sufficient to assess the consequences of the downturn in LTx activity is debatable.

Interestingly, similar findings were obtained in the US [19], where listing of LTx candidates and LTx procedures dropped by 40% and 28%, respectively, compared to 28% and 13% for the heart. Moreover, whereas heart transplantation activity recovered rapidly after the first COVID-19 wave, the same was not true for LTx.

Several reasons may explain the 31.27% decrease in French LTx activity during the pandemic [18] . In France, during the first

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Table 1
The ten criteria required to consider lung transplantation in patients with end-stage lung disease dur to COVID-19, adapted from Cypel and Keshavjee [34].

	Candidates
	Age under 65 years
	Single organ dysfunction
	Allow sufficient time for lung recovery (4 to 6 weeks)
	Radiological evidence of irreversible lung disease
	Patient awake and able to discuss transplantation
	Patient participating in physical rehabilitation
	Absence of typical contra-indication to LTx
	Absence of SARS-CoV2 infectivity
	Centre
	Centre experienced in performing high-risk LT
	Access to a broad-donor pool and low waiting-list mortality

COVID-19 wave in early 2020, the LTx task force of the French pulmonology society (Société de Pneumologie de Langue Française) decided that LTx should be performed only in patients on the high-priority waiting list and in those deemed to require the procedure urgently [12]. This decision was based on the need to ensure optimal use of the few operating rooms that had not been converted into COVID-19 ICUs, concern about shortage of critical-care devices such as ventilators and extra-corporeal membrane oxygenation pumps, and the potential risks associated with exposure of LTx candidates or recipients to COVID-19 infection in crowded ICUs. However, these concerns were not the main reason for the drop in LTx procedures. Donations fell in France by 16% from 1 March to 31 July 2020 compared to the same periods in 2018 and 2019. The decrease was similar in the US [20] and even higher in the UK [21]. A key reason for the decrease in donations is that ICU beds were not available for donors (as for recipients) [22, 23]. Also, the very tight first lockdown in France may have reduced the number of donors who died from traumatic injuries, as reported in the US [20]. Finally, the discarding of organs from 14 potential donors (1% of potential donors) between 1 March and 31 July due to positive SARS-CoV2 tests made a minor contribution [22].

Efforts were made to maintain LTx activity despite the pandemic. The UK set up COVID-light hospitals, where only patients requiring elective care and free of the SARS-CoV-2 virus were treated. One of these centres continued to offer care to all LTx candidates but performed only 7 LTx procedures (58% of all LTx procedures in the UK) between 1 March and 31 May 2020, and LTx activity dropped by 77% compared to 2019 [21]. Clearly, the COVID-light approach is insufficient to tackle the LTx challenges raised by the pandemic. Alternative strategies must be devised and tested to protect LTx candidates and recipients as we prepare for further COVID-19 waves or COVID-19 endemicity.

Lung transplantation (LTx) for end-stage COVID-19 pneumonia

LTx has recently emerged as a therapeutic option for refractory acute respiratory distress syndrome caused by COVID-19 [24–32]. We identified 26 reported cases. The disease was extremely severe, with patients having no evidence of lung healing, and 24 requiring ECMO for a median duration of 39.5 days [IQR, 21.3–65.5]. The pre-LTx ECMO durations were shortest for the earliest patients (range, 10–19 days) [24, 25]. In the following reports, more time was given to the possibility of improvement (pre-LTx ECMO duration range, 17–180 days) [26–28, 30–32]. Surgery was challenging, with dissection difficulties in 7 patients [26, 27, 33] and high blood-product requirements. The outcomes were encouraging, with a median post-operative follow-up of 90 days [IQR, 52–144] in 23 patients and only 3 patients dying [25, 26, 30].

The hazards of LTx in this particular setting are still debated [34–36]. The healing potential of the lung is not predictable. A comprehensive pre-transplant assessment, notably of the patient's neurocognitive and psychological profile, is difficult to achieve. These patients cannot give informed consent to LTx. We do not know whether an acceptable strategy to ensure the optimal use of scarce organs is to perform LTx in patients with immediately life-threatening disease, after a pared-down pre-LTx evaluation, but not in those whose condition is severe and chronic but stable. Ten criteria for selecting patients with COVID-19 for consideration as LTx candidates have been suggested (Table 1) [34]. New data may prompt a modification of these criteria within the next few months.

Finally, acute respiratory distress due to any cause [37] including COVID-19 [38] has been reported to induce lung fibrosis. Time will tell whether sequelae from COVID-19 will represent a significant indication for LTx.

Thus, the COVID-19 pandemic has had a global and severe adverse effect on LTx recipients, candidates, and procedures. In the field of transplantation, LTx appears particularly vulnerable. Although the overwhelming of the entire healthcare system was unpredictable, LTx physicians must now use their newly acquired experience to develop master plans for addressing healthcare system crises, including future COVID-19 waves. Understanding how different countries and healthcare systems respond to COVID-19-related challenges may improve pandemic preparedness, including the strategies devised to maintain transplantation activity in order to prevent the loss of patient life-years.

Declarations of Competing Interest

None.

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