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Beware the Deus Ex Machina of COVID-19



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As our society marks several months since the World Health Organization declared the coronavirus disease 2019 (COVID-19) outbreak a pandemic, we note the development of encouraging strategies to slow the spread of disease, streamline resource allocation, and adapt the cutting edge of critical care medicine to answer the challenges brought to bear by severe respiratory syndrome coronavirus type 2 (SARS-CoV-2). Despite these efforts and accomplishments, clinicians on the front lines continue to encounter patients with severe acute respiratory distress syndrome (ARDS) who fail to improve despite aggressive therapy such as extracorporeal membrane oxygenation (ECMO). Therefore, we were interested to read 3 non-peer-reviewed reports of patients undergoing double-lung transplantation for COVID-19-associated respiratory failure.

In the field of lung transplantation, we are accustomed to providing a treatment of last resort. Medications may be costly, operations may be risky, but few other modern medical interventions represent true zero-sum choices in which the opportunity to treat 1 patient comes at the expense of treating another. Even before the COVID-19 pandemic, the United States was experiencing a shortage in donor lungs relative to the number of patients awaiting transplants; it is too early to assess the full impact of this crisis on organ availability, but it is difficult to envision a scenario in which a widespread transmissible respiratory illness increases the number of suitable donor lungs relative to need.

Nonetheless, it is unsurprising that lung transplantation is being explored for patients with COVID-19. This operation has proven life changing for tens of thousands of patients with chronic pulmonary diseases, and although lung transplantation for ARDS is uncommon, it is not without precedent.¹ In addition to its potential clinical advantages, this reapplication of lung transplantation would continue to foster hope for the most devastated patients with COVID-19 and for society at large as we work toward a vaccine and improved medical therapies. However, we identify several reasons to remain circumspect in the consideration of lung transplantation for COVID-19-induced ARDS.

Organ allocation is predicated in part on achieving long-term benefit for the recipient. At present, the natural history of COVID-19 in general and for transplant recipients in particular remains uncertain in several key

respects. Although there are many tests for active SARS-CoV-2 infection and antibody development, whether they can reflect true resolution of disease or prove the absence of extrapulmonary viral reservoirs is unknown. There is also uncertainty surrounding the efficacy of humoral immunity in preventing reactivation of or recurrent infection. Even if these risks are low for the general population, transplant recipients (especially the newly immunosuppressed) represent a distinct and vulnerable risk pool. This view is supported by emerging data from the New York State transplant consortia demonstrating that transplant recipients have COVID-19-related mortality disproportionate to that observed in the general public. Technical success notwithstanding, it is simply too soon to quantify the midterm or long-term effects of COVID-19 on transplant recipients, including lung transplant recipients in the handful of cases that have occurred.

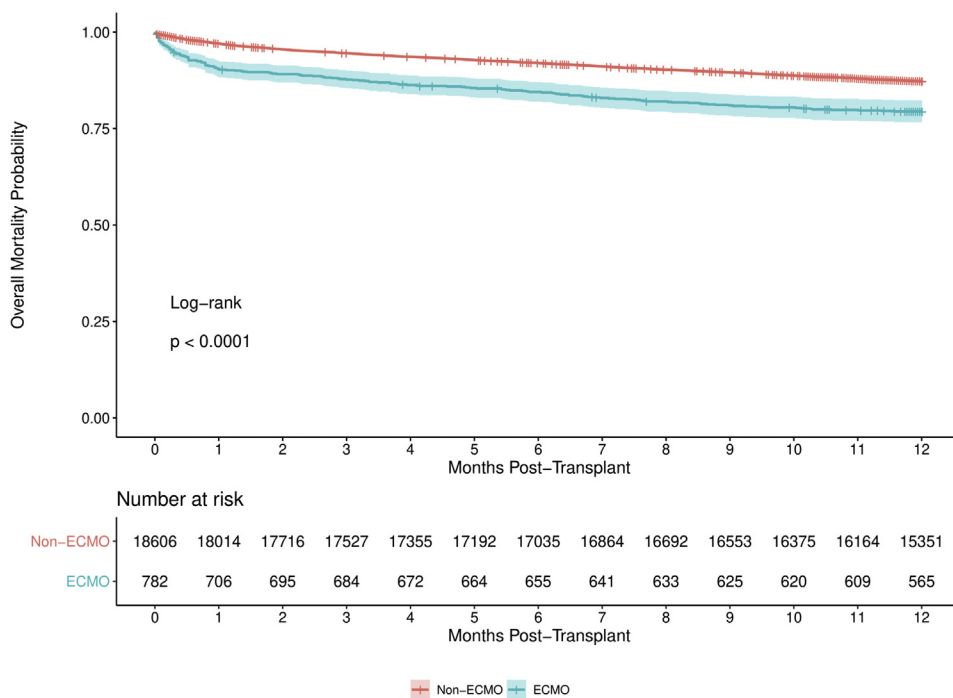
We recognize that in the presence of critical illness, immediate solutions can sometimes take precedence over these longer-term considerations. ECMO, once itself seen as a bold new rescue measure, is now applied as an intermediary between respiratory failure and transplantation as cure. However, the manner in which this is implemented has a significant impact on transplant outcomes. Historically, patients who were sick enough to require ECMO as a bridge to transplantation have fared more poorly than standard transplant recipients (Figure 1; Appendix). Our groups and other highly specialized centers have since developed bridging practices to ameliorate this gap, thereby offering safer transplants to previously high-risk patients.² Notably, these protocols emphasize gradual physiologic optimization and rely on a careful perioperative rehabilitation program: these are luxuries that may not be tolerated by many critically ill patients with COVID-19. There may still be distinct clinical circumstances under which salvage transplantation (ie, transplantation for worsening status despite maximal therapy) is warranted. On balance, however, years of experience and data have shown that patients in this difficult scenario face outcomes that resemble early efforts to transplant patients bridged with

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The Appendix can be viewed in the online version of this article [<https://doi.org/10.1016/j.athoracsur.2020.08.001>] on <http://www.annalsthoracicsurgery.org>.

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Figure 1. Difference in probability of 1-year survival between lung transplant recipients undergoing extracorporeal membrane oxygenation (ECMO) vs all other lung recipients over a 10-year period ending June 1, 2018.



ECMO support more closely than those achieved with modern bridging practice. As stewards of donor organs, transplant physicians have a responsibility to ensure that these organ are offered to patients who are likely to derive the greatest benefit.

Consideration of transplantation in refractory COVID-19-associated ARDS may also be driven, in part, by the risks and perceived futility of prolonged venovenous (VV) ECMO support. Afflicted lungs have been shown to incur severe alveolar damage with microangiopathy,³ leading to concern for irreversible loss of function. However, our experience has shown that VV-ECMO can be safely and effectively deployed for weeks to months, thus facilitating recovery even in patients with severe cases of ARDS. We previously studied patients with ARDS who were treated with ECMO for more than 3 weeks (median, 36 days; interquartile range, 24 to 68 days) and found noninferior survival to hospital discharge compared with patients receiving less than 3 weeks of ECMO support (73% vs 57%; $P = .5$).⁴ Recovery of native lung function from ARDS after more than 100 days of VV-ECMO has also been described.⁵ More recently, as of the writing of this report, at our institution in New York City (NYU Langone Health) we have brought COVID-19 patients from critical pulmonary failure to recovery after more than 21 days ($n = 11$), more than 42 days ($n = 6$), days more than 56 days ($n = 4$), more than 63 ($n = 3$), and more than 112 days ($n = 1$) of ECMO therapy (unpublished data). We suggest that, on the basis of these and similar data in ARDS,⁶ many of these patients will improve, and the pursuit of transplantation should not be a forgone conclusion.

The COVID-19 pandemic has tested many of our resources, but perhaps none is more important than hope.

We applaud the heroic efforts put forth to serve the patients hit hardest during these uncertain times. For previously healthy patients with isolated respiratory illness, lung transplantation may appear to be the natural solution to an otherwise intractable disease—we certainly identify with good faith efforts to offer our best treatments to patients even in exceptional circumstances. For this reason, we look forward to the valuable insights to be gained from these unique experiences. Until those are available, for the uncertainties and limitations described, we urge caution and temperance in considering the inclusion of lung transplantation in the broader armamentarium against COVID-19 at this juncture.

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