Lung Transplantation for COVID-19 Acute Respiratory Distress Syndrome: The British Columbian Experience With New Disease Pathology

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Lung transplantation is a life-saving treatment for patients with end-stage lung disease. COVID-19 has been associated with a severe and rapid decline in pulmonary function, in which case lung transplantation has been described to be effective. We herein describe 9 patients who underwent lung transplantation for COVID-19 acute respiratory distress syndrome, of whom 6 were bridged with extracorporeal membrane oxygenation (ECMO). The median time of pre-operative observation periods was 54 days to ensure no lung function recovery and the time to wean off extracorporeal membrane oxygenation was 3 days. Patients had comparable short-term survival outcomes to non-COVID-19 lung transplant recipients at our institution during the same time period. Lung transplantation for COVID-19-associated lung disease is feasible with comparable short-term outcomes and may liberate patients from extracorporeal supports.

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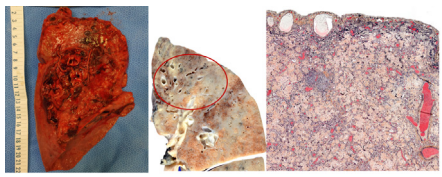

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Central Message

Lung transplant for COVID-19 associated lung disease is feasible with comparable short-term survival to non-COVID-19 lung transplant recipients and may liberate patients from extracorporeal supports.

Perspective Statement

Six patients required ECMO bridging to lung transplantation with lengthy pre-operative observation periods to ensure no lung function recovery [median = 54 days]. Median time to wean off ECMO was 3 days and patients had comparable short-term survival outcomes to non-COVID-19 lung transplant recipients. Additional cases are required to predict the ideal length of pre-transplantation observation period.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global pandemic, halting normalcy within medical practice. Most affected individuals experience mild illness, however, 5%-10% require intensive care unit (ICU) admission for respiratory support.[1-3] In this critically ill subgroup, mortality has been reported to be as high as 60%.[4,5] Emerging international data supports that 45% of affected patients will develop pulmonary fibrosis with irreversible loss of lung function.[6] Lung transplantation is a recognized treatment for end-stage lung disease,[7] however, there is a paucity of data on short- and long-term outcomes following lung transplantation in the setting of COVID-19 associated acute respiratory distress syndrome (COVID-ARDS).[8-14]

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Over the following decades, COVID-19 induced pulmonary fibrosis of varying degrees is suspected to interplay with progressive pulmonary function decline for a subset of acute and chronic lung disease patients, ultimately necessitating lung transplantation. Therefore, a detailed understanding of whether this disease process varies from other etiologies of end-stage lung disease requiring transplantation is necessary to ensure best care for COVID-19 patients with resultant acute and chronic pulmonary function deterioration. The study objective is to present the preliminary experience of our regionalized lung transplantation center for COVID-ARDS.

METHODS

From March 2020 to October 2021 a retrospective observational study was conducted at Vancouver General Hospital (VGH), the regionalized quaternary level high volume lung transplantation center from the province of British Columbia (BC), Canada. Institutional research board approval was obtained (UBC REB #H21-02343). Consecutive cases of lung transplantation for COVID-ARDS were prospectively identified. Transplant candidacy was guided by an abbreviated format of the Vancouver Lung Transplant Program eligibility criteria. Candidates must have single-system failure, radiological evidence of irreversible lung disease, and 2 consecutive negative COVID-19 polymerase chain reaction (PCR) tests. For patients with COVID-ARDS on extra-corporeal membrane oxygenation (ECMO) support, it is not yet clear what the ideal time is to allow for recovery prior to considering transplantation. Until such data exists, the best alternative is the consensus of involved intensivists, respirologists, infectious disease experts and thoracic surgeons. Once a unanimous decision has been attained to move forward with transplant evaluation, a comprehensive assessment of maladaptive and non-compliance behavior was conducted along with non-invasive oncologic work up and infectious disease screening. Social workers and various close contacts were involved in the work-up to ensure appropriate patient selection.

The requirement of informed consent for research participation was upheld. Data was collected on baseline demographics, in addition to prior clinical variables of interest including perioperative extracorporeal membrane oxygenation support pre-transplant with median pre-transplant, organ ischemic time, primary graft dysfunction (PGD), 30-day and 90-day survival, and post-operative adverse events. Continuous variables are reported as medians (range), and categorical variables as counts (percent). Statistical analysis was conducted using RStudio PBC Version 1.4.1717 Boston, Massachusetts.

RESULTS

A total 9 bilateral lung transplants were performed for COVID-ARDS during the study period, 6 (67%) of which required ECMO bridging to lung transplantation (EBLTx) Table 1. Median recipient age was 52 with median BMI of 25.3. One patient had underlying sarcoid pulmonary disease, however, was not awaiting lung transplantation prior to COVID-19 infection. Five (56%) patients were Indo-American, 3 (33%) were Caucasian and 1 (11%) was Chinese. All 9 patients underwent successful bilateral lung transplantation without acute rejection and 6 (67%) met diagnostic criteria for PGD. Median intra-operative blood transfusions was 8 units of packed red blood cells (pRBC) and 2 patients (22%) required a re-operation.

Table 1. Patient and Operative Characteristics

Patient Characteristics	
Age (median, IQR)	52 [31, 59]
Female sex, n (5)	2 (22%)
BMI (median, IQR)	25.3 [21.6, 28]
Underlying lung disease n, (%)	1 [11%]
Ethnicity n, (%)	
Indo-American	5 [56%]
Caucasian	3 [33%]
Chinese	1 [11%]
Operative Characteristics	
ECMO pre-transplant n, (%)	6/9 [67%]
Successful ECMO bridge to transplant BLTx (%)	6/7* [100%]
Double lung transplant	9/9 [100%]
Left lung ischemic time (median, IQR)	370 min [213, 680 min]
Right lung ischemic time (median, IQR)	320 min [182, 407 min]
D ECMO Pre-transplant† (median, IQR)	54 [32, 98]
D ECMO Post-transplant ECMO* (median, IQR)	3 [0, 25]
Ventilator d post lung transplant (median, IQR)	21 [1, 77]

BMI, body mass index; ECMO, extra-corporeal membrane oxygenation; IQR, interquartile range; Min, minutes.
*Seven patients on ECMO for COVID-19 were listed for transplant during the study period. One patient recovered and did not undergo transplantation.
†n = 6. Only patients requiring ECMO are included.

Median pre-operative ECMO time was 54 days [IQR 32, 98]. Post-transplantation ECMO and mechanical ventilation were weaned at a median time of 3 and 21 days, respectively. There were no mortalities at 30 days, however there was 1 (11%) 90-day mortality. At the conclusion of the study period, 7 (78%) patients had been discharged either to a rehabilitation facility or home. Median post-transplantation ICU and hospital lengths of stay were 29 and 53 days, respectively. Non-COVID-19 EBLTx patients had a median pre-operative time on ECMO, median post-operative time on ECMO and median post-operative time on mechanical ventilation of 3, 2 and 6 days, respectively. Median post-operative ICU length of stay in non-COVID EBLTx patients was 29 days, and 56 days for total post-operative time in hospital Table 2.

Review of the explanted lung pathologic specimens demonstrated a common alteration of a chronic fibrosing interstitial pneumonia with multiple secondary / background changes. All lungs demonstrated firm, pale zones of loss of normal

Table 2. Clinical Outcomes, n (%)

Event	n=9
30-d survival	9 [100%]
90-d survival	8 [89%]
Reoperation (all-cause)	2 [22%]
Reinitiation of ECMO	0 -
Reintubation	0 -
CRRT	1 [11%]
DVT	4 [44%]
PE	1 [11%]
Sepsis	3 [33%]
Acute rejection n (%)	-, 0%
Primary Graft Dysfunction n (%)	6 [67%]
Post-transplant ICU LOS, d (median, IQR)	29 [4-104]
Post-transplant Hospital LOS, d (median, IQR)	53 [18, 160]

CRRT, continuous renal replacement therapy; DVT, deep vein thrombosis; ECMO, extra-corporeal membrane oxygenation; ICU, intensive care unit; LOS, length of stay; PE, pulmonary embolism.

parenchymal markings however these changes showed variable distribution. Many cases showed a diffuse pattern, however in others a distinct zonation could be appreciated (Figure S1). Microscopically, the dominant pattern was a combination of non-specific interstitial pneumonia (NSIP) with a spectrum of clear architecture-sparing mild interstitial fibrosis that often blended with more coarse interstitial thickening and what was interpreted as atelectatic compression.

In 3 (33%) cases depicted in figures S2 and S3, the dominant histopathological reaction was considered within the spectrum of nonspecific interstitial pneumonia (NSIP), both with fine and coarse expansion of the alveolar septal walls, and associated with variable amounts of parenchymal compression, interpreted as a form of atelectasis. Rare foci of residual organizing airspace exudates (organizing pneumonia, [OP]) were identified in 2 (22%) cases. In 1 of these, the architectural density of these structures could be considered as "cicatricial" OP.[15] Patchy diffuse alveolar hemorrhage (DAH) was identified in 2 (22%) cases, as were rare small vascular thrombi. A solitary case (11%) was remarkable for the presence of bilateral irregular cavities, with Candida species identified both on the silver stain for fungus as well as on microbiological culture.

DISCUSSION

COVID-19 has entrenched itself internationally as it inconspicuously assumes an endemic state. The long-term end-stage pulmonary outcomes of this viral illness have yet to be reported on an international scale. Due to a scarcity of such data, it is important for lung transplantation centers globally to report preliminary institutional experience.

Based on our British Columbian experience of lung transplantation for COVID-ARDS, we observed 2 distinct sub-sets of transplantation recipients for the new disease. The first observed clinical course is that in which a patient with COVID-19 develops the complication of COVID-19 associated pneumonia and progressively declines to a state of irreversible, end-stage pulmonary fibrosis requiring artificial life support. These patients are at a distinct crossroad of pursuing comfort care and death vs lung transplantation. Six (66%) of our transplanted patients followed this common course, with a median preoperative time on ECMO of 54 days during which they had never indicated potential for recovery during weaning trials. Other transplant centers have reported varying time of EBLTx,[12-14] however it remains difficult to predict the ideal time for lung transplantation in this cohort.[16] During the study period, 1 patient with COVID-19 respiratory failure was listed for lung transplantation, however, his clinical status improved after 56 days on ECMO and he was subsequently delisted. A recent systematic review of non-COVID-19 patients undergoing bridge to lung transplant reports median times of pre-transplant ECMO runs ranging from 3.2 to 16 days among included studies.[17] The drastic difference between our median length of EBLTx and those reported in the literature supports the extended assessment for restorable lung function performed in our population given the uncertainty of COVID-19's natural history. Additional data from COVID-19 patients undergoing lung transplantation will help better predict the ideal time for transplantation at which spontaneous recovery is unlikely and further assessment of recovery on ECMO is detrimental to post-operative recovery and morbidity. Similarly to other Canadian centers,[16] our institution's consensus is to allow for a minimum observation period of 6 weeks during which no lung function recovery is appreciated prior to pursuing lung transplantation.

The second clinical course reported in our series is that in which a patient with COVID-19 develops progressive pulmonary fibrosis and sufficient parenchymal destruction to warrant lung transplantation, yet they can manage activities of daily living (ADLs) with typical supports for chronic end-stage pulmonary fibrosis. Three patients in this study group experienced such disease courses. One patient, previously followed for sarcoid pulmonary disease with stable pulmonary function was diagnosed with COVID-19 7 months prior to his representation during which he underwent transplantation. At the 2-month follow-up from initial hospital admission for COVID pneumonia, FVC and DLCO were found to be 49% and 30%, worsened from the prior values of 60% and 43%, respectively. Despite this decline in respiratory function, he managed his ADLs until representing in respiratory distress, requiring ICU admission and lung transplantation. The other 2 patients were initially admitted to hospital, 1 requiring optiflow 100% and the other necessitating mechanical ventilation. Both experienced improved respiratory function over time, but their respiratory support requirements plateaued at 100% optiflow on exertion. Extensive work up revealed no reversible causes, ultimately leading to a transplant team consultation. Superficially, this subset of recipients is comparable to transplant candidates with others forms of fibrosing lung disease. Our cohort, along with evidence from other large transplant centers has depicted short-term outcomes comparable to non-COVID-19 related lung transplantation.[11,13,14] We anticipate that as COVID-19

lingers within society, a surplus of individuals similar to this subset of patients will present for lung transplant assessment due to pulmonary function decline following initial recovery from an acute fibrosing infection.

Time on pre-operative ECMO, mechanical ventilation, and ICU and hospital length of stay differed between COVID-19 patients and those with non-COVID-19 lung disease who were bridged to lung transplant at our institution during the same time period (Table S1). Despite the notable differences in length of pre-operative ECMO and post-operative mechanical ventilation, median post-transplantation ICU and hospital length of were not drastically different. The lengthier post-transplantation mechanical ventilation seen in the EBLTx COVID-19 group can likely be attributed to the lengthier pre-operative ECMO runs, resulting in increased deconditioning. Comparisons in ECMO-related outcomes between these groups should be made with caution since the groups differ in the intent of outcome (recovery vs transplantation) at the time of ECMO initiation and due to the small cohort sizes.

Challenges With ECMO-Bridged Patients

All the EBLTx COVID-19 patients experienced pulmonary fibrosis to a severity of having minimal pulmonary reserve leading to rapid clinical deterioration despite ECMO support. Therefore, pre-habilitation efforts and physiotherapy were not feasible. The decision to pursue transplantation despite the lack of rehabilitation remains controversial.[14,16] Our ICU and hospital lengths of stay are longer than patients who did undergo pre-habilitation efforts.[14]

Patients on ECMO for COVID-19 lung disease present unique challenges to the healthcare team, amplified in our study population due to the prolonged ECMO runs compared to non-COVID-19 bridge to lung transplant patients.[17] Prolonged runs of ECMO induce states of bleeding diatheses causing frequent hemorrhage from tracheotomy and cannulation sites, enhancing the risk of infection and need for transfusion. Similar to other centers, our patients experienced episodes of bleeding into the pleural space and airways, some requiring interventional radiology (IR) guided coiling and surgery.[10,13] Nonetheless, only 2 of 9 (22%) patients in our study group required a re-operation, both of which were due to postoperative intra-thoracic hemorrhage. The rate of re-operation following EBLTx during the same period of time for non-COVID-19 patients at our institution was 43% (3/7), 2 of which were due to hemothoraces (2/7, 29%) and 1 due to bowel ischemia (1/7, 14%). Although the rates of intrathoracic post-operative hemorrhage requiring intervention are similar in the non-COVID-19 and COVID-19 bridge to lung transplant cohorts, confident comparisons of post-operative hemorrhage and re-operation rates cannot be made due to the small size of our study cohort.

The technical aspect of COVID-19 lung explant was not dissimilar to traditional lung explant apart from challenges associated with hypocoagulable states. Mean units transfused were 1.5 and 11.2 for non-bridged and bridged patients, respectively. Post-operative venous thromboembolism (VTE) prophylaxis was selectively administered to patients who showed no evidence of post-operative hemorrhage, as dictated by their hemoglobin level and chest X-Rays. Intravenous heparin was started on post-operative day 1 if no signs of hemorrhage were present. One patient in the EBLTx group (1/6, 17%) did not receive immediate post-operative VTE prophylaxis due to significant intra-operative bleeding and the use of a thoracic negative pressure wound dressing with intentions of a relook and closure within 48 hours of BLTx.

Transplant Candidacy

For both subsets of patients in our cohort, transplant candidacy was guided by an abbreviated format of the Vancouver Lung Transplant Program eligibility criteria. Candidates must have single-system failure, radiological evidence of irreversible lung disease, and 2 consecutive negative COVID-19 polymerase chain reaction (PCR) tests. The decision to pursue lung transplantation in our EBLTx cohort was complicated by the fact that all patients required substantial sedation to maintain stable hemodynamics. Therefore, consent and information on the availability of social supports was acquired from the patient's substitute decision maker, which differs from other high volume centers.[14,16] We acknowledge this is highly controversial, and these cases of consent were taken with great discomfort. Given the unique context in which patients cannot consent, are exhibiting no evidence of potential recovery and palliation remains the sole alternative, we consider the surrogate decision maker's consent a rational substitute. However, we would argue that this approach can only occur in centers with a high-volume experience with a well-managed wait list so that decisions to include such transplant candidates do not negatively affect those previously on the list.

Pathologic Characteristics

COVID-19 affected lungs were noted to have a unique amalgamation of characteristics on gross specimen review although all explanted lungs demonstrated increased density and significant volume loss, some conforming to the size of the surgeon's hand in the deflated state (Fig S4). Although some variability in the distribution and extent of histopathological disease was noted, all cases demonstrated severe replacement of the normal lung parenchyma by established fibrosis that was considered generally within the spectrum of fibrosing NSIP and accompanied by lesser amounts of other pathologies probably reflecting individual combinations of initial lung injury severity, host immune / inflammatory response, establishment of intercurrent infections, presence and effect of pharmacotherapies, ventilation strategy and ECMO support (if utilized). Most initial pathological reports of COVID-19 pulmonary disease were, by necessity, relegated to post-mortem examinations and as expected, the dominant pathological pattern was that of acute lung injury, diffuse alveolar damage (DAD) type.[18] With time, and the accrual of survivors proceeding to transplantation, a wider spectrum of pathology has been revealed with post-acute lung injury fibrosis being described. The interstitial fibrosis

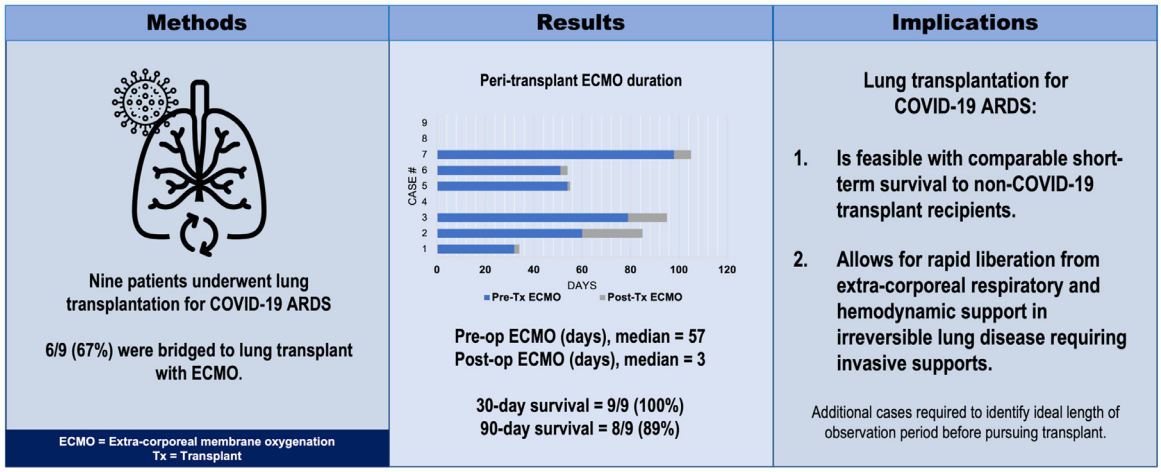

Figure 1. Lung transplantation for COVID-19 acute respiratory distress syndrome.

described in these cases includes a high number of cases classified as NSIP, at least as a histopathological pattern.

Based on the BC experience, lung transplantation for COVID-19 pulmonary fibrosis was not seen to adversely affect the mortality rate of the cohort of patients on the waiting list given the stability of that rate during the period under observation. This outcome was, in part, governed by the ongoing expansion of our lung transplant program that was able to accommodate the additional burden of end-stage lung failure cases.

CONCLUSION

The 9 lung transplantations performed for COVID-ARDS by the Vancouver General Hospital lung transplant team have shown feasibility of lung transplantation in this patient population with short-term outcomes comparable to non-COVID-19 related lung transplantation (Fig. 1). We anticipate increased necessity of lung transplantation for the new disease of COVID-19 associated end-stage pulmonary fibrosis. Further follow up and international collaboration are required to document long term outcomes and ensure best care.

SUPPLEMENTARY MATERIAL

Scanning this QR code will take you to the article title page to access supplementary material.

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REFERENCES

1. Liu Y, Mao B, Liang S, et al: Association between ages and clinical characteristics and outcomes of coronavirus disease 2019. Eur Respir J 55:2001112, 2020
2. Huang C, Wang Y, Li X, et al: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395:497–506, 2020
3. Remuzzi A, Remuzzi G: COVID-19 and Italy: What next? Lancet 395:1225–1228, 2020
4. Yang X, Yu Y, Xu J, et al: Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir Med 8:475–481, 2020
5. Arentz M, Yim E, Klaff L, et al: Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. JAMA 323:1612–1614, 2020
6. Hama Amin BJ, Kakamad FH, Ahmed GS, et al: Post COVID-19 pulmonary fibrosis; a meta-analysis study. Anna Med Surg 77:103590, 2022
7. Myles PS, Snell GI, Westall GP: Lung transplantation. Curr Opin Anaesthesiol 20:21–26, 2007
8. Hawkins RB, Mehaffey JH, Charles EJ, et al: Lung transplantation for severe post-coronavirus disease 2019 respiratory failure. Transplantation 106:1381–1387, 2021
9. King CS, Mannem H, Kukreja J, et al: Lung transplantation for patients with COVID-19. Chest 161:169–178, 2022
10. Bharat A, Manchuca T, Querrey M, et al: Early outcomes after lung-transplantation for severe COVID-19: A series of the first consecutive cases from four countries. Lancet Resp Med 9:487–497, 2021
11. Bharat A, Querrey M, Markov NS, et al: Lung transplantation for patients with severe COVID-19. Sci Transl Med 12:eabe4282, 2020
12. Magnusson JM, Silverborn M, Broome M, et al: Long term extracorporeal membrane oxygenation bridge to lung transplant after COVID-19. Ann Thorac Surg 113, 2022
13. Yeung JC, Marcelo C, Chaparro C, et al: Lung transplantation for acute COVID-19: The Toronto lung transplant program experience. Canadian Med Assoc J 193:e1494–e1497, 2021
14. Kurihara C, Manerikar A, Querrey M, et al: Clinical characteristics and outcomes of patients with COVID-19–associated acute respiratory distress syndrome who underwent lung transplant. JAMA 327:652–661, 2022
15. Yousem: Cicatricial variant of cryptogenic organizing pneumonia. Human Pathol 64:76–82, 2017
16. Cypel M, Keshavjee S: When to consider lung transplantation for COVID-19. Lancet Respir Med 8:944–946, 2020
17. Chiumello D, Coppola S, Froio S, et al: Extracorporeal life support as bridge to lung transplantation: A systematic review. Crit Care 19:19, 2015
18. Fernández-Cardinal P, Lorente JA, Barragán-Ballén A, et al: Acute respiratory distress syndrome and diffuse alveolar damage. new insights on a complex relationship. Ann Am Thor Soc l14:844–850, 2016

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