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A center experience with lung transplantation for COVID-19 ARDS

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A B S T R A C T

COVID-19 can cause irreversible lung damage from acute respiratory distress syndrome (ARDS), chronic respiratory failure associated with post COVID-19 de novo fibrosis or worsening of an underlying fibrotic lung disease. Pregnant women are at increased risk for invasive mechanical ventilation, extracorporeal membrane oxygenation, and death. The Centers for Disease Control and Prevention reported more than 22,000 hospitalizations and 161 deaths for COVID-19 in pregnant women. Between August 2020 and September 2021, five patients underwent bilateral lung transplant (LT) for COVID-19 ARDS at the Henry Ford Hospital in Detroit, Michigan. De-identified demographics data, clinical characteristics, perioperative challenges, explanted lung pathology, and post-transplant outcomes are described. In post-hospitalization follow-up (median survival 273 days), we see improving endurance and excellent lung function. One patient did not survive to hospital discharge and succumbed to complications 5 months after LT. We report the first cases of bilateral LT in two postpartum women.

1. Introduction

The mortality for COVID-19 ARDS remains high in the range of 20%–40% in critically ill patients on mechanical ventilation and extracorporeal membrane oxygenation (ECMO). For patients with refractory ARDS, mortality on veno-venous ECMO (vvECMO) was similar to prepandemic historical data during the first wave [1,2]. Preliminary data showed worse mortality on COVID-19 patients on vvECMO during subsequent waves of the pandemic [3]. Favorable short-term outcomes of lung transplantation (LT) have been reported. The first report in March 2020 described three Chinese patients that underwent successful bilateral LT for COVID-19 ARDS [4]. Others reported on their experience from centers in China, United States, Canada, Italy, Austria, and India [4–9]. The largest single center in the United States described 100% survival at 30-days post-bilateral LT for COVID-19 ARDS in 3 patients [10]. A recent review of published and unpublished literature described the effectiveness of LT in 21 patients with COVID-19 ARDS [7]. Additional cases of LT have been performed but are unreported. A query of the United Network for Organ Sharing identified COVID-19 as the diagnosis in over 200 LT cases through November 2021 since the United Network for Organ Sharing implementation of COVID-19 as a diagnosis in October 2020 [11].

Abbreviations: ARDS, acute respiratory distress syndrome; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IV, intravenous; LT, lung transplantation; mRNA, messenger RNA; vvECMO, veno-venous extracorporeal membrane oxygenation.

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Table 1
Clinical characteristics pre and post lung transplant. BLT bilateral lung transplant; IMV invasive mechanical ventilation; ECLS extracorporeal mechanical support with ECMO; CNI calcineurin inhibitor; MMF mycophenolate mofetil; PGD primary graft dysfunction; FEV1 forced expiratory volume, FVC forced vital capacity. Patient 5 only had one spirometry since LT (*).

Patient	1	2	3	4	5	Total
Age - years	47	37	61	31	35	Median 37 (IQR 33, 54)
Gender	Male	Male	Male	Female	Female	Male (60%)
Ethnicity	White	White	Arab American	White	White	
Body-mass index - kg/m^2	33.5	36.9	26.92	37.5	37.5	Median 36.9 (IQR 30.2, 37.5)
ABO group	O+	A+	O+	A+	A+	
Comorbidities	None	Asthma	None	Post-partum, ulcerative colitis	Post-partum, asthma	
COVID-19 characteristics						
Treatment for COVID-19						
-Remdesivir	X	X	X	X	X	100%
-Corticosteroids	X	X	X	X	X	100%
-Tocilizumab	X		X		X	60%
-Convalescent plasma				X		20%
-Monoclonal antibodies						0%
-Antibiotics for pre-LT infection	X		X	X		80%
COVID-19 complications						
-Bacterial pneumonia		X	X		X	60%
- Pneumothorax				X	X	40%
-Acute kidney injury				X		20%
-Venous thromboembolism					X	20%
-Right ventricular dysfunction			X			20%
Indication for transplantation	COVID-19 ARDS	COVID-19 ARDS	COVID-19 ARDS	COVID-19 ARDS	COVID-19 ARDS	
Time from COVID-19 to transplant - days	62	114	59	57	54	Median 54 (IQR 55.5, 88)
COVID-19 diagnosis to listing	62	106	55	47	40	Median 55 (IQR 43.5, 84)
COVID-19 diagnosis to negative PCR	42	85	50	33	47	Median 47 (IQR 37.5, 67.5)
COVID-19 diagnosis to ICU admission	11	22	8	10	6	Median 10 (IQR 7, 16.5)
COVID-19 diagnosis to IMV	21	16	12	16	4	Median 16 (IQR 8, 18.5)
COVID-19 diagnosis to vvECMO	47	15	45	32	47	Median 45 (IQR 23.5, 47)
Time from IMV to transplant - days	40	100	47	30	50	Median 47 (IQR 35,75)
Time on ECLS to transplant - days	15	99	14	25	7	Median 32 (IQR 10.5, 62)
Time on wait list - days	4	37	4	10	5	Median 5 (IQR 4, 23.5)
ECLS						
VV ECMO (single site, dual lumen cannula)	X				X	
VV ECMO (two cannula)		X	X	X		
Transplantation characteristics						
Lung allocation score	88.05	89.77	85.78	87.26	87.7	Median 87.7 (IQR 86.4, 88.8)
CMV serostatus	D+/R+	D+/R-	D-/R+	D+/R-	D+/R-	
Tracheostomy at time of transplant	Yes	Yes	Yes	Yes	Yes	100%
Type of transplantation	BLT	BLT	BLT	BLT	BLT	100%
Clamshell incision	X	X	X	X	X	100%
VAV ECMO perioperative				X	X	40%
Total ischemic time - hours	6.2	7.0	4.7	4.6	5.9	Median 5.68 (IQR 4.65, 6.6)
Post-transplantation characteristics						
Prolonged ECMO support						0%
Grade of PGD (0,1, 2, 3, UG)	3	3	3	0	0	
Duration of MV - days	6	161	15	17	49	Median 17 (IQR 10.5, 105)
ICU LOS post LT - days	32	161	21	26	52	Median 32 (IQR 23.5, 106.5)
Total LOS post LT - days	56	161	36	26	67	

(*continued on next page*)

Table 1 (*continued*)

Patient	1	2	3	4	5	Total
						Median 56 (IQR 31, 114)
Anti-rejection regimen						
Induction	X		X	X	X	80%
Calcineurin inhibitor	X	X	X	X	X	100%
Mycophenolate mofetil	X		X	X	X	80%
Corticosteroids	X	X	X	X	X	100%
Length of follow up post-discharge - days	188	0	266	331	98	Median 227 (IQR 143, 298)
Current status	Alive	Dead	Alive	Alive	Alive	
Days alive post LT	244		302	357	165	Median 273 (IQR 204, 329)
Lung function (last value)	4.13		3.95 (97%)	3.25 (95%)	2.23 (54%)*	
FVC L (% pred)	(99%)		3.19 (104%)	2.43 (84%)	2.05 (61%)*	
FEV1 L (% pred)	3.22 (98%)					

Most of the publications have included male patients, below 60 years of age, and report an early survival rate of 95%. None have included pregnant women with COVID-19 ARDS. Compared to the general population, pregnant women with COVID-19 are at increased risk of severe disease including pre-eclampsia, venous thromboembolism, need for intensive care unit (ICU) care and mechanical ventilation [12–14].

We describe the clinical characteristics and outcomes of the first 5 patients that underwent LT at our center for COVID-19 ARDS, including 2 pregnant women who received transplants in the immediate postpartum period.

2. Materials and methods

The Henry Ford Health System Institutional Review Board approved this case series as minimal-risk research using data collected for routine clinical practice (#14953). Requirement to obtain informed consent for the analysis of consecutive cases was waived by the institutional review board.

SARS-CoV-2 infection was confirmed by nasopharyngeal real-time polymerase chain reaction (PCR) and computed tomography scan of the chest showed changes typical of COVID-19 pneumonia in all cases. Patients with respiratory failure on mechanical support were considered for LT if no evidence of improvement at least 28 days from onset of COVID-19 pneumonia and 2 negative PCR tests for SARS-CoV-2 including one sample from the lower respiratory tract. Patients were evaluated by a multidisciplinary transplant team for determination of non-recovery of lung function and eligibility for transplantation as per expert opinion and endorsed by the International Society for Heart and Lung transplantation criteria [15,16].

Retrospective review of electronic medical records with analysis of demographics, baseline comorbidities, COVID-19 related data, pre- and post-transplant related characteristics and outcomes. We included all patients transplanted for COVID-19 ARDS from January 2021 to September 2021. Only bilateral orthotopic LT was performed.

3. Results

Three males and 2 postpartum females with single organ failure underwent bilateral LT. Median age was 37 years. Clinical characteristics are summarized in Table 1. All patients received systemic corticosteroids (dexamethasone or methylprednisolone), and intravenous (IV) remdesivir for COVID-19 pneumonia. Three were transfers from other facilities for LT evaluation. All were intubated prior to transfer and only one was already on vvECMO at the time of transfer. The remaining two were placed on vvECMO shortly after arrival to our hospital.

Standard ICU management for ARDS included lung protective ventilation, paralytics, systemic corticosteroids, and prone positioning in all cases. Antibiotic therapy, tocilizumab and therapeutic anticoagulation were also used in some patients. Eventually, all patients required ECMO for refractory severe hypoxic respiratory failure.

Poor lung mechanics on invasive mechanical ventilation with radiographic evidence of ground-glass opacities, airspace consolidation and lung fibrosis: pneumatocele, subpleural reticulations and traction bronchiectasis were seen in all patients. Ventilator-associated pneumonia with an identifiable organism by standard lower respiratory culture was diagnosed in 2 patients. vvECMO was instituted with the goal of bridging to transplant in 3 cases, whereas in 2 patients ECMO was used as bridge to recovery but due to dependence on mechanical support without evidence of lung recovery, LT was performed with ECMO as a bridge. Tracheostomy was placed in all patients. Median time to LT from COVID-19 diagnosis was 59 days (interquartile range [IQR]: 54–62 days). Mechanical ventilation median duration was 47 days and median ECMO duration was 32 days (range 7–99 days). Attempts to wean sedation was associated to worsening respiratory status with frequent ventilator dyssynchrony, worsening hypoxia and hemodynamic instability. Median time on the wait list was 5 days (IQR: 4–23.5 days). A substitute decision-maker consented for LT in most cases. Rehabilitation potential and strong social support were absolute inclusion criteria. Postoperative ECMO decannulation was possible in all cases. Donated grafts were from deceased brain death donors and negative for SARS-CoV-2.

Following our perioperative immunosuppression strategy, all but 1 patient received induction immunosuppression with 1 g of

methylprednisolone, 750 mg of mycophenolate and 20 mg IV of basiliximab (dose repeated on day 4 post-LT). Maintenance immunosuppression with addition of tacrolimus on post-LT day 4 and prophylaxis is standard for our center. Patient 2 in Table 1 did not receive basiliximab and mychophenolate induction immunosuppression as he had history of Enterococcus and *Escherichia coli* bacteremia during his ICU stay prior to LT, and his donor lungs grew *Burkholderia gladioli* and *Candida glabrata* from bronchoalveolar lavage.

Two of our patients were pregnant women with COVID-19 infection. Our first case was a 31-year-old woman, gravida 1, para 0, with history of obesity and ulcerative colitis. She was hospitalized with COVID-19 and severe pre-eclampsia. Seven days later, at 36 weeks gestation she vaginally delivered a healthy female infant. She was treated with dexamethasone 6 mg daily, IV remdesivir, IV unfractionated heparin, vitamin C, zinc and received antibiotics for endometritis. Due to disease progression, she was intubated and put on mechanical ventilation on day 16 after confirmation of COVID-19. Five days later vvECMO was initiated for refractory severe hypoxic respiratory failure secondary to COVID-19 ARDS. She had a right spontaneous pneumothorax that was drained with a small-bore chest tube. Due to hemodynamic instability, VAV ECMO was necessary 4 days before listing. After approximately 5 weeks on ECMO and 10 days after listing, she received a bilateral LT in January 2021. The patient was unvaccinated for COVID-19.

Another 35-year-old woman, gravida 1, para 0, with history of asthma, obesity and nephrolithiasis was hospitalized for COVID-19 pneumonia. She was treated with methylprednisolone, IV remdesivir and IV tocilizumab but had progressive respiratory failure and was intubated on hospital day 4. Due to non-reassuring fetal status in the setting of COVID-19 ARDS, she underwent cesarean section, giving birth to a healthy female infant at 35 weeks of gestation, four days after COVID-19 diagnosis. She developed pneumonia due to Serratia species and pulmonary embolism treated with IV cefepime and full-dose anticoagulation, respectively. She required placement of a chest tube for left-sided pneumothorax. Despite treatment, she failed to show recoverable lung function. She was cannulated for vvECMO as a bridge to LT 43 days after invasive mechanical ventilation. Seven days after she was listed, she received a bilateral LT from a deceased donor. The patient was unvaccinated for COVID-19.

Both pregnant patients were obese, and in their thirties, which have been described as risk factors for poor outcomes. Pre-eclampsia in the first patient and pulmonary embolism in the second have been described as complications of COVID-19 in pregnancy and are associated to increase mortality. Both patients also developed pneumothoraces before bilateral LT.

All 5 patients had radiologic and pathologic confirmation of end-stage irreversible COVID-19 pneumonia. Explanted pathology in all cases showed interstitial fibrosis, diffuse alveolar damage, diffuse hemorrhage and one case of fibrosing non-specific interstitial pneumonia (Fig. 1). Pulmonary hypertension was seen in 3 cases.

One male patient did not survive. He developed primary graft dysfunction 3 (PGD) as well as other complications: hemorrhagic pancreatitis, deep vein thrombosis, right main bronchus anastomosis dehiscence, pseudoaneurysm of left colic artery and empyema. He eventually died from septic shock secondary to Gram negative bacteremia and candidemia 5 months after bilateral LT and 6 months after confirmed COVID-19 pneumonia.

Despite high doses of narcotics/sedations pre-transplant, all survivors were free of narcotics at time of hospital discharge with no signs of narcotic dependence. Four patients have post-hospitalization follow-up demonstrating excellent lung function in the three

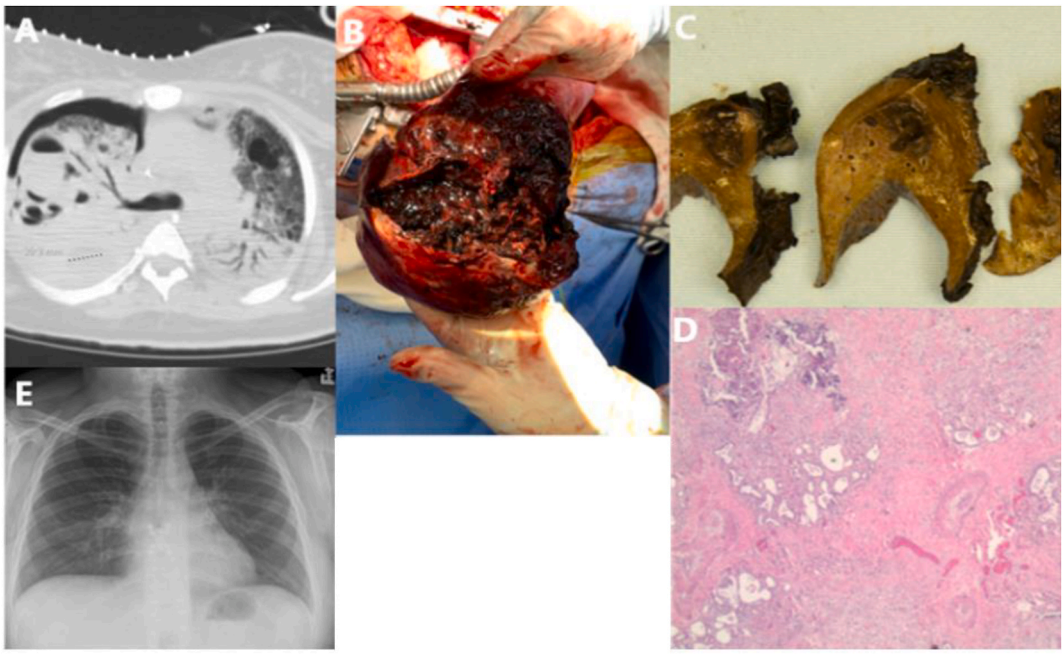

Fig. 1. A., CT chest of patient 4, eleven days before her bilateral LT shows right pneumothorax, consolidation, bronchiectasis, and cystic lesions. In B. and C., her explanted lungs are small with consolidation and extensive hemorrhage. D., Histopathology shows densely fibrotic lung with residual effaced alveolar airspace. The pulmonary arteries exhibit hypertensive changes (20X). E., CXR on the same patient approximately 9 months post bilateral LT.

patients with longer follow-up. Median follow-up post-hospitalization is 227 days (range, 98–331 days). All 4 have stable radiographic findings without identification of clinically significant acute allograft rejection (acute cellular rejection A2 or higher, or antibody mediated rejection) in surveillance bronchoscopies.

4. Discussion

We describe the characteristics and outcomes of the first 5 patients that underwent LT at our center for COVID-19 ARDS, including 2 pregnant women in the immediate postpartum period.

For COVID-19 ARDS, general guidelines recommend careful selection of patients for LT in cases of irreversible, end-stage COVID-19 lung disease based on clinical grounds and evidence of extensive fibrotic lung disease as demonstrated on computed tomography [15]. Undetectable presence of SARS-CoV-2 by PCR in 2 respiratory samples obtained 24 hours apart and including one from alveolar lavage or lower respiratory tract is necessary [16]. In most reported cases, transplant has been performed in individuals under 65 years of age with single organ dysfunction (lungs) and after allowing enough time for lung recovery [10,15]. Most cases have been performed off ECMO (Table 2) [4–6,8,9]. Rehabilitation potential prior to acute illness must be present. Other absolute contraindications for LT in the general population of end-stage lung diseases must not be present [17,18]. Most LTs for COVID-19 ARDS have been bilateral due to the frequent presence of pulmonary hypertension and superimposed bacterial pneumonias. LT in this setting is recommended to be performed in centers with experience in high-risk transplantation (including experience on ECMO) due to the challenging perioperative and postoperative care with expected prolonged ICU stay [6]. All of our 5 cases of COVID-19 ARDS met the general guidelines described above for LT.

The characteristics of our 5 cases are comparable to that reported so far, with ages ranging from 31 to 61 years **(Table 2).** All had single organ (lung) failure, with time from COVID-19 diagnosis of 54–114 days and time on ECMO support of 7–99 days. The period of follow-up is longer in our report, up to 11 months.

Table 2
Summary of global reports of lung transplantation for COVID-19 respiratory failure (published cases and current study).

Author Country Year	No. of Cases	Age years	Sex	Type of LT	COVID-19 diagnosis to LT (days)	IMV	ECMO support (days)	Pre-LT ECMO type	Intra-op ECLS	ECMO Post-op	ECMO Post-op (days)	Follow-up (months) and outcomes
Bharat et al. USA/ 2020	3	28	F	BLT	40	X	32	VV		X	17	
		62	M	BLT								
		43	M	BLT								
Chen JY et al. China/ 2020	3	66	M	H-L	42	X	15	VAV	VA ECMO			died intra-op
		58	M	BLT	37	X	7	VV	VA ECMO	X	1.5	
		73	M	BLT	44	X	19	VV	VA ECMO	X	1.6	
Lang et al. Austria/ 2020	1	44	F	BLT	58	X	35	VV	VA ECMO	X	3	
Han W et al. China/ 2020	2	66	F	BLT	30					X	5	
		70	M	BLT	35					X		
Maniar et al. USA/ 2021	1	51	M	BLT	84	X	82	VV		X	3	
Gok et al. USA/ 2021	2	69	M	BLT	57							
		63	M	BLT	68							
Yeung et al. Canada/ 2021	3	60	M	BLT	59	X	17	VV				5
		53	M	BLT	88	X	60	VV				4
		48	M	BLT	98	X	92	VV				4
Hawkins et al. USA/ 2021	1	57	M	BLT	50	X	14	VV	CPB			
Current study USA 2021	5	47	M	BLT	62	X	15	VV	VA ECMO			8
		37	M	BLT	114	X	99	VV	VA ECMO			5 (died)
		61	M	BLT	59	X	14	VV	VA ECMO			10
		31	F	BLT	57	X	25	VV, VAV	VA ECMO			11.9
		35	F	BLT	54	X	7	VV	VA ECMO			5.5

Note: LT, lung transplantation; BLT, bilateral lung transplantation; IMV, invasive mechanical ventilation; ECMO, extracorporeal oxygenation; ECLS, extracorporeal life support; CPB cardiopulmonary bypass

Our report is the first to describe successful LT for COVID-19 ARDS in post-partum women. In both cases the infants were born healthy. Women especially those infected with the SARS-CoV-2 delta variant during pregnancy are likely to have worse outcomes due to the increased risk of severe COVID-19 [12–14]. There is also an increased risk for adverse pregnancy and neonatal outcomes, including preterm birth and admission of their neonate(s) to an ICU [13,19,20]. At the time of their COVID diagnosis, safety of messenger RNA (mRNA) vaccines was not well established and like in our 2 cases, most pregnant women in the United States at that time were not vaccinated. Current safety data of mRNA vaccines in pregnant women, and on women planning to get pregnant, support the Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists recommendation for COVID-19 vaccination in this patient population [21,22].

LT for COVID-19 presents additional challenges. Participation of the patient on decision making, comprehensive psychosocial evaluation, pre-transplant education and rehabilitation is often not possible due to the severity of their illness and limitations of being in infection isolation. Sedated COVID-19 ARDS patients, who were not able to engage in decision making process, wake with shock, fear, disbelief of what they had undergone. Waking up after unknowingly undergone lung transplantation can be traumatic for patients and has resulted in a variety of concerning psychosocial outcomes. We have found a spectrum of psychological symptoms and diagnoses, ranging from acceptance and gratitude to severe depression, anxiety, and anger. Patients have reported symptoms consistent with an acute stress reaction (which can develop into PTSD over time). The seemingly insurmountable challenge of accepting what had happened to them and poor coping can significantly negatively impact the patient's ability to appropriately engage in their care, leading to a myriad of additional problems and complications.

Regarding medical decision making, ethical principles of beneficence, non-maleficence, and justice were certainly taken into consideration; however, with the patient unable to engage in decision making, their freedom to choose (autonomy) has been taken away [23]. It can be agreed that all involved proceeded with what they felt was in the best interest of the patient. However, the inability to demonstrate one's autonomy in such a life changing decision can also impact the patient's ability to cope with and accept transplantation and its associated lifestyle changes. Given these unique circumstances, close follow up with a psychologist or other mental health provider is recommended to support patients as they adjust to post-transplant life.

The diagnosis of COVID made a consistent and typical rehabilitation course not possible due to the innate medical complexities of the disease (intubation, sedation, paralytics, prone positioning, and high doses of inotropic support) [24]. Physical and occupational therapy in our patients were inconsistent and many times limited to bed exercises due the patients' frequently changing medical status, and the various tests and procedures being performed. This was further restricted by pain, edema, and endurance. ICU myopathy, deconditioning, and delirium were common occurrences in these patients.

4.1. Limitations

This is a retrospective single-center cohort study of 5 patients. The literature reviewed only peer-reviewed publications of case reports/series without systematic data collection and insufficient information on post-LT outcomes. This short follow-up does not provide an answer regarding long-term outcomes.

5. Conclusion

In the United States, most LT for COVID-19 is for irreversible severe COVID-19 ARDS. LT for ARDS is reserved for the minority of carefully selected patients dependent on extracorporeal life support. As we and others have reported, short-term survival appears to be good; however, long-term outcome data is yet to be described. It will be important for centers without transplant programs to establish a close line of communication with transplant centers and for transplant centers to streamline the process to allow transferring of a very ill patient that on initial assessment could be considered for this lifesaving procedure. Acknowledging the commonly present complications and the shortcomings of an incomplete evaluation, a very careful selection of patients can save some lives.

Declaration of competing interest

The author(s) declare that there is no conflict of interest.

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