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Clinico-Radiological-Pathologic Profile and Outcomes of Lung Transplant in Post−COVID-19 Phenotype: A Single Center Experience

Unmil Shah[a*], Vijil Rahulan[a], Srinivas Ravipati[a], Sharanya Kumar[b], Anoop Mohandas Kamath[b], Santosh Kori[b], Sushant Panda[b], Vivek Singh[a], Pradeep Kumar[b], Prasanna Gopalam[b], I. Satish Rao[c], Abhiram Kalle[c], Manish Dass[d], Prem Anand John[d], Mahesh Bangalore Nagaraj[d], Prabhat Dutta[b], and Sandeep Attawar[d]

[a]Department of Transplant Pulmonology, Krishna Institute of Medical Sciences, Secunderabad, India; [b]Department of Transplant Anesthesiology and Critical Care, Krishna Institute of Medical Sciences, Secunderabad, India; [c]Department of Pathology, Krishna Institute of Medical Sciences, Secunderabad, India; and [d]Department of Transplant Cardio-Thoracic Surgery, Krishna Institute of Medical Sciences, Secunderabad, India

ABSTRACT

Background. Lung transplantation (LTx) has come as hope for select patients with post-COVID acute respiratory distress syndrome (ARDS). It has a different phenotype with unique challenges. We aimed to bring out our experience with and outcomes of LTx for post-COVID ARDS.

Methods. This study is retrospective case series from a single center in India. All the patients with post-COVID end stage lung disease (ESLD) who underwent bilateral LTx between 1st May 2020 and 30th August 2021 were included. LTx was performed following no improvement with optimal medical management with adequate time provided for recovery. Information relating to demographics, comorbidities, pretransplant status, perioperative parameters, gross and histopathological findings of explanted lungs, posttransplant morbidity, and mortality were analyzed.

Results. This study included 23 patients. The median age of the patients in this study was 42 years and 20 participants were men (87%). The mean duration of intensive care unit stay was 15.83 ± 6.61 days. Mortality was observed among 8 participants (34.78%). Mean survival time was 34.54 weeks. Among the 8 patients who expired, the cause of death was sepsis for 6 patients (75.0%), neurologic cerebrovascular accident for 1 patient (12.5%), and cytomegalovirus for 1 patient (12.5%). All the deaths were reported in primary graft dysfunction grade 2 & 3 category. No rejections were observed on first and third month surveillance biopsies.

Conclusions. LTx is the definitive option for survival in select patients with severe post−COVID-19−associated ESLD. This study brings out various challenges involved in such phenotypes and also observations in postoperative recovery.

As per the World Health Organization, as of January 2022, India has had 35,875,790 confirmed COVID-19 cases, including 484,213 mortalities [1]. Worldwide, there have been 308,458,509 confirmed cases of COVID-19, including 5,492,595 deaths [1]. Current evidence suggests acute respiratory distress syndrome (ARDS) is the most common pulmonary complication of the COVID-19 [2]. Various mechanisms of lung injury in COVID-19 have been described, with both viral and immune-mediated mechanisms being implicated [3]. A smaller percentage of patients with more severe disease require ventilatory support and are admitted to high dependency and intensive care units (ICUs). In a Chinese study of 1099 hospitalized COVID-19 patients, the use of mechanical ventilation, death, or admission to an ICU occurred in 67 patients (6.1%), including 5.0% who were admitted to the ICU, 2.3% who underwent invasive mechanical ventilation, and 1.4% who

*Address correspondence to Unmil Shah, MD. Department of Transplant Pulmonology, Heart and Lung Transplant Institute, Krishna Institute of Medical Sciences, Minister Road, Krishna Nagar Colony, Begumpet, Secunderabad, Telangana 500003. E-mail: drunmilshah@gmail.com

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died. Extracorporeal membrane oxygenation (ECMO) was performed in 5 patients with severe disease (0.5%) [4]. The mortality associated with COVID-19 is considerable—in a large UK study by Vlachos et al, 18% of them were admitted to the ICU, 52% met criteria for ICU outreach team activation, and 61% had treatment limitations placed during their admission. Hospital mortality was 26% and ICU mortality was 34% [5], concluding that COVID-19 is associated with a high burden of mortality for patients treated in the ward and the ICU hospital mortality was independently associated with increasing age, male sex, history of chronic kidney disease, increasing baseline C-reactive protein level, and dyspnea at presentation. In a review by George et al, COVID-19-related ICU mortality has been reported to be between 16% and 78% [6]. Lung transplantation (LTx) has been offered as a life-saving therapy for select patients with COVID-19 who have persistent respiratory failure despite several weeks or months of support in the ICU. Most patients who progress to severe respiratory failure do have comorbidities that may be a challenge in deciding transplant candidacy. Many will develop secondary complications such as renal dysfunction, muscle wasting, or other organ failure while on ECMO as mentioned by Cypel and Keshavjee [7]. LTx can be considered as a salvage therapy for carefully selected patients who have severe treatment-refractory ARDS as described by Lang et al [8].

So far most of the published studies are based on anecdotal case reports and small sample size case series. To understand the outcomes and factors associated with the outcomes is challenging owing to such small sample size. The experiences of other centers with higher volumes of data may throw light on these aspects, if not providing scientifically robust inferences. These studies may establish a strong platform and provide meaningful insights for further large scale and scientifically robust studies.

Here we report a retrospective study, a single center experience of 23 LTx done in recipients with post-COVID fibrotic progressive end stage lung disease (ESLD) . We also describe challenges faced preoperatively as well as postoperatively for such recipients. This is presumably the first case series from a single center in India describing LTx experience in such phenotypes with reasonable outcomes.

METHODS AND MATERIALS

Patients received treatment according to the local standard of care from a multidisciplinary COVID-19 care team. Referral to the LTx team was made when at least 4 weeks had elapsed since the onset of respiratory failure and there was no evidence of lung recovery as agreed by the multidisciplinary team as per criteria elaborated by the Toronto group [7]. Not all patients with severe COVID-19 who were treated at the respective centers were referred to LTx after 4 weeks. Common reasons that precluded LTx evaluation included multiorgan failure, inability to assess neurologic status if the patient was unresponsive or not awake, complications such as sepsis or stroke, and general contraindications relevant to LTx. Each patient was then evaluated by the LTx team with standard evaluation protocol and considered a candidate for transplant if other programmatic criteria were met, according to the International Society for Heart and Lung Transplantation guidelines. Patients with multiorgan failure were excluded from LTx evaluation for COVID-19. All patients underwent extensive pulmonary rehabilitation for optimization while on waitlist. All recipients were operated with conventional clamshell incision. All recipients were transplanted on converting venovenous (VV) to venoarterial (VA) ECMO intraoperatively. Intraoperatively, all patients received induction immunosuppression with Inj Basiliximab (20 mg) along with Inj Methylprednisolone (1000 mg IV). Postoperatively, depending on PaO2/FiO2 ratios, hemodynamics, lung compliance, radiological findings, and cardiac function, ECMO weaning was initiated. All recipients postoperatively were started on a 3-drug immunosuppression regimen of steroids, tacrolimus, and mycofenolate mofetil. Routine surveillance bronchoscopies were performed regularly to monitor anastomotic healing, collect broncho-alveolar lavages if required, and so on. All recipients postoperatively underwent pulmonary rehabilitation, early mobilization, and judicious nutritional support.

LTx performed between May 2020 and August 2021 in patients with post-COVID fibrotic progressive ESLD (post-ARDS) were taken into consideration. We collected data relating to patient demographics, comorbidities, pretransplant status (clinical, radiological, medical course, and indications for LTx), perioperative parameters, gross and histopathological findings of explanted lungs, posttransplant morbidity, and mortality. Chest computed tomography was done for all patients preoperatively showing common radiological signs of consolidations, reticular changes, interstitial fibrosis and patchy ground glass opacities. (Fig 1). This study received approval from an internal ethics committee in compliance with the ethical standards set forth in the Helsinki Congress (Approval no: KIM S/ECB MHW 202 I/26.03).

RESULTS

Characteristics of Study Population

A total of 23 bilateral LTx in such phenotypes were performed between May 2020 and August 2021. All of them were transferred from tertiary care hospitals across India to our Transplant Hospital. All of them were endotracheal reverse transcription-polymerase chain reaction−negative for SARS-CoV-2 infection for 2 samples taken at least 24 to 48 hours apart preoperatively. The median age of patients in this study was 42 years, with 3 people aged 60 years or above (13%) (Table 1). Twenty were men (87%). Five subjects had normal body mass index (21.7%), 13 were overweight 13 (56.5%), and 5 were obese (21.7%). Out of 23 recipients, 8 recipients were B positive (34.7%), 5 were A positive (21.7%), 9 were O positive (39.1%), and 1 was AB positive (4.3%). All 23 recipients received Remdesivir, steroids, and anticoagulants as part of their COVID treatment. Among the study population, Hypertension was the most common morbidity among 7 (30.4%), followed by diabetes among 3 (13%) and coronary artery disease among 2 (8.7%) participants. The mean ventilation and ECMO days were 48.87 $\pm$ 23.43 and 43.78 $\pm$ 24.25 respectively (Table 2).

Out of 23 recipients, 22 patients were supported with VV ECMO (conventional dual cannulae fem-ijv). All 22 patients were awake while on ECMO. One patient had ESLD post-COVID leading to respiratory failure requiring high flow nasal cannula with 40 lit flow.

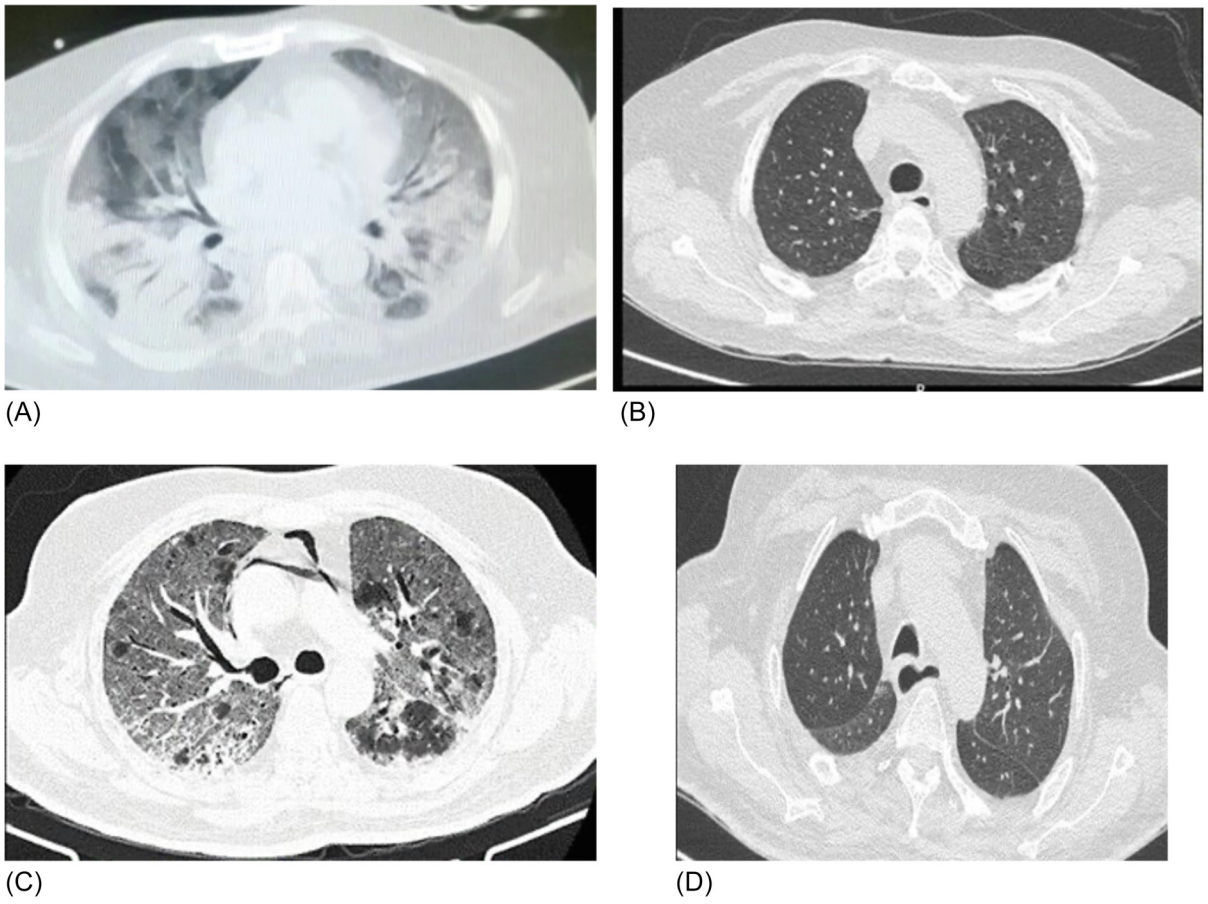


Fig. 1. Radiological features of (A) (Pre-Transplant) of participant 1. (B) (Post-Transplant) of participant 1. (C) (Pre-Transplant) of participant 2. (D) (Post-Transplant) of participant 2.

Table 1. Baseline Demographic and Clinical Characteristics of Study Population (N = 23)

Baseline Parameters	Summary
Age (y; median IQR)	42 (34, 58)
Age group, no. (%)	
<60 y	20 (87)
≥60 y	3 (13)
Sex, no. (%)	
Male	20 (87)
Female	3 (13)
BMI, no. (%)	
Normal (18-24.99)	5 (21.7)
Overweight (25-29.99)	13 (56.5)
Obese (≥30)	5 (21.7)
Prevalence of comorbities, no. (%)	
Hypertension	7 (30.43)
Diabetic mellitus	3 (13)
Coronary artery disease	2 (8.7)

BMI, body mass index; IQR, interquartile range.

Preoperative and Intraoperative Parameters

The mean ischemia time on right and left sides were 356 ± 78.58 and 232.35 ± 81.23 minutes respectively. All recipients required multiple blood product transfusions intraoperatively; the median number of blood products used were (11 (10,13)). The median number of cryo, FFP, leukocyte depleted packed red blood cells and random donor platelets were (2 (1,2), 4 (2,4), 3 (2,4), and 3.5 (2,4)) respectively (Table 2).

Postoperative Parameters

At 72 hours posttransplant, 4 (17.4%) participants each had primary graft dysfunction (PGD) grade 0 and grade 1, 7 had grade 2 (30.4%), and 8 had grade 3 PGD (34.8%) (Table 3). The mean duration of ICU stay was 15.83 ± 6.61 days, and the mean hospital stay duration was 62.74 ± 32.42 days. Posttransplant morbidity included acute kidney injury requiring Renal Replacement Therapy in 6 recipient (26%), critical illness neuropathy or neuromuscular weakness in 13 recipients (56.5%),

Table 2. Summary of Preoperative and Intraoperative Parameters (N = 23)

Baseline Parameters	Summary
Preop parameters	
Pretreatment ventilation (d)	48.87 ± 23.43 (0, 90)
Pretreatment total ECMO (d)	43.78 ± 24.25 (0, 93)
Total ECMO days (wk) (%)	
<6 weeks	12 (52.2)
≥6 weeks	11 (47.8)
Characteristics of explant	
Left explant volume (mm^3)	1051.09 ± 444.08 (157.50, 2058)
Right explant volume (mm^3)	1461.29 ± 534.67 (726, 2700)
Left explant lung weight (g)	462.52 ± 137.54 (213, 684)
Right explant weight (g)	539.09 ± 154.9 (210, 895)
Ischemia time left (min)	356 ± 78.58 (200, 512)
Ischemia time right (min)	232.35 ± 81.23 (94, 381)
Intraop total no. of blood products (Median [IQR])	**11 (10, 13)**
Intraop cryo (no. of units)	2 (1, 2)
Intraop FFP (no. of units)	4 (2, 4)
Intraop LDPRBC (no. of units)	3 (2, 4)
Intraop RDP (no. of units)	3.5 (2, 4)

ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; IQR, interquartile range; intraop, intraoperative; LDPRBC, leukocyte depleted packed red blood cells; preop, preoperative; RDP, random donor platelets.

Table 3. Summary of Postoperative Parameters (N = 23)

Postoperative Parameters	Summary
PGD grade at 72 h (%)	
0	4 (17.4)
1	4 (17.4)
2	7 (30.4)
3	8 (34.8)
Post-LTx parameters	
No. of days in ICU	15.83 ± 6.61 (6, 28)
Hospital stays (d)	62.74 ± 32.42 (16, 150)
Post LTx duration of follow up (mo; Median [IQR])	4 (3, 9)
Status at final follow-up (%)	
Alive	15 (65.2)
Expired	8 (34.78)
Cause of death (n = 8) (%)	
Sepsis	6 (75.0)
Neurologic CVA	1 (12.5)
CMV	1 (12.5)

CMV, cytomegalovirus; CVA, cerebrovascular accident; ICU, intensive care unit; LTx, lung transplantation; PGD, primary graft dysfunction.

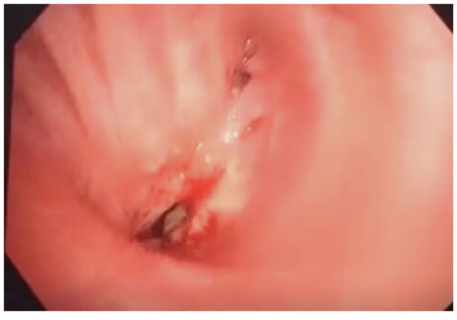
and airway anastomotic stenosis requiring balloon dilatation in 8 recipients (34%) with SEMS-covered stenting done subsequently in 5 recipients (21%) (Fig 2). Five recipients (21%) were discharged with tracheostomy while the rest were successfully decannulated in wards. All recipients were mobilizing well at time of discharge.

Pathology of COVID-19 Lungs

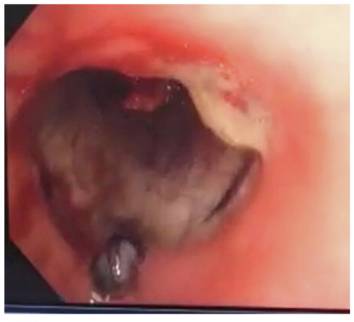
Pathologic correlation: macroscopic. The following macroscopic features were commonly noted: external surface pleura showing, in Fig 3A patchy fibrotic areas and irregular nodularity, cut surfaces showing patchy subpleural nodules were observed; in Fig 3B, cystic changes and few dilated thick-walled bronchi were observed; in Fig 3C shrunken fibrotic lungs were observed; and in Fig 3D a lung with a cavity was observed (the weight of explanted lungs ranged from 210-895 g).

Pathologic correlation: histopathological. The following various histopathological findings were noted (Fig. 4):

a. Nonspecific interstitial pneumonia-like changes with focal spatial heterogeneity;
b. Focal areas of usual interstitial pneumonia-like changes, areas of interstitial fibrosis with chronic inflammation and hemorrhage;
c. Alveolar spaces and bronchial lumen showing luminal neutrophilic abscess;
d. Diffuse alveolar damage with hyaline membrane formation;
e. Vessels showing luminal narrowing with medial hypertrophy, vessels showing thrombi in lumen;
f. Focal areas showing temporal heterogeneity and microhoneycombing, prominent perivascular edema with stromal fibroblastic proliferation;
g. Focal areas of peribronchiolar fibrosis and areas of mucosal ulceration, sections from cystic areas showing dilated bronchioles with denuded or sloughed off epithelium, interstitial spaces with diffuse lymphomononuclear infiltrates;



(A)



(B)

Fig. 2. Airway complications. (A) Left anastomotic stenosis. (B) Right mainstem bronchial SEMS-covered stent.

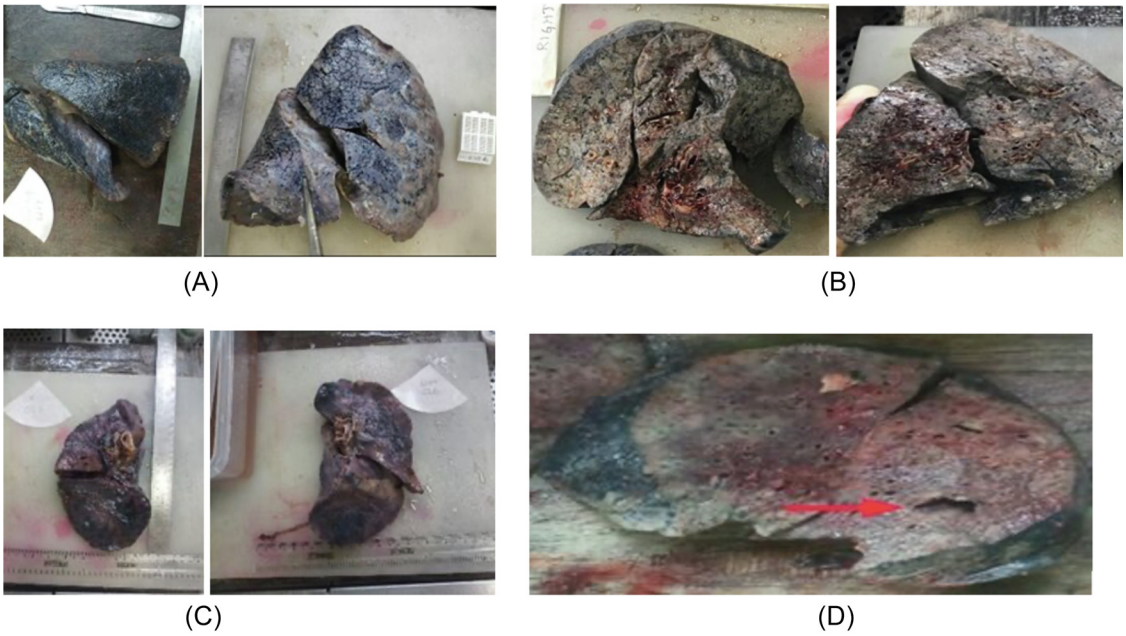


Fig. 3. (A) Consolidated lungs with irregular nodularity. (B) Cystic changes with thick-walled bronchi. (C) Shrunken lungs. (D) Lung with cavity

h. Residual alveolar lumina showing neutrophilic abscess, foamy histiocytic collection, with focal macrophage proliferation, prominent squamous metaplasia;
i. Type 2 pneumocyte hyperplasia, patchy areas of organizing pneumonia, myogenic metaplasia with fibroblastic foci, some sections showing honeycombing with denudation of lining epithelium, lymph nodes showing reactive hyperplasia;
j. One of the explanted lungs showing infarcted areas with large colonies of fungi with narrow septate, branching hyphal forms with parallel walls showing both tissue- and angio-invasion (highlighted on Gomori's Methenamine Silver stain) proving to be *Aspergillus* species;
k. One of the explanted lungs also showing scattered necrotizing granulomas warranting antituberculosis treatment posttransplant.

Survival and Cause of Mortality

The median post-LT duration of follow-up was 4 (3, 9) months. Out of 23, 15 participants were alive (65.22%) and 8 participants were dead (34.78%). Among the 8 patients who expired, the cause of death was sepsis for 6 patients (75.0%), neurologic cerebrovascular accident for 1 patient (12.5%), and cytomegalovirus for 1 patient (12.5%) (Table 3). Among the 6 sepsis deaths, 2 were related to the *Klebsiella pneumoniae* multidrug resistant organism, carbapenem-resistant strains, and multiorgan dysfunction, 1 recipient had vancomycin-resistant enterococci sepsis, and 3 recipients had fungal sepsis (non-*Albicans candida*). We didn't see any episodes of acute cellular rejection or antibody-mediated rejection posttransplant in 1- and 3-month surveillance biopsies.

Kaplan-Meier Survival Analysis (in Weeks)

The mean survival time for the patients was 34.540 weeks. The median survival time for the patients was 20 weeks (ie, 50% of the survival was achieved in 20 weeks [Fig 5]).

Factors associated with mortality

Mortality was higher among patients aged 60 and above compared with patients <60 years of age (66.67% vs 30%, $P = .27$). Patients with any comorbidity had a higher proportion of mortality (50% vs 26.67%, $P = .37$). Patients with preoperative ECMO days of 6 weeks or more also had higher mortality (45.5% vs 25%, $P = .30$). Even among patients with preoperative ECMO of more than 6 weeks, 54.5% survived. The median number of preoperative ventilation days, ECMO days, and the number of intraoperative blood products was higher among patients who died. All of the deaths were reported in the PGD grade 2 & 3 category, with no deaths within the PGD 0 & 1 category. The median postoperative hospital days were lower in the mortality group, suggesting intrahospital mortality (Table 4).

Among the recipients, 14 had positive blood cultures (60.86%). One recipient showed *Pseudomonas*, 3 had *K pneumoniae*, 2 had *Enterococcus*, 1 had *Enterobacter*, 1 showed *Stenotrophomonas maltophilia*, 1 showed *Elizabeth kingiea*, 1 showed *Chryseobacterium*, and 4 showed *Candida auris*.

DISCUSSION

We performed 23 bilateral LTx in recipients affected with post-COVID fibrotic progressive ESLD. We treated the patients who underwent LTx for COVID-19 with a typical three-drug

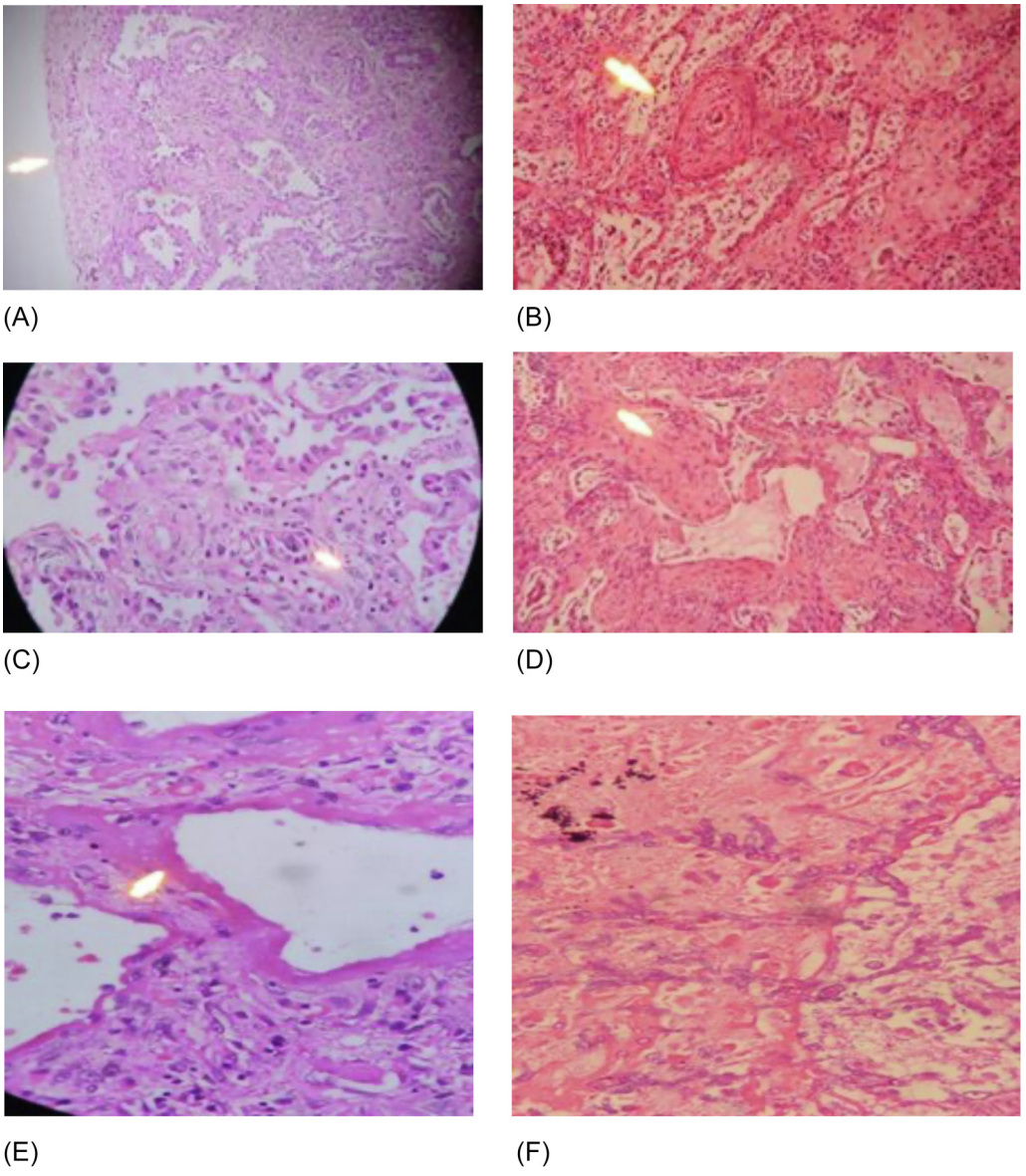


Fig. 4. Histopathological changes. (A) Arrow for subpleural fibrosis. (B) Concentric vascular thickening with thrombus. (C) Pneumocyte hyperplasia with multinucleation. (D) Fibroplastic Foci. (E) Honeycombing with interstitial fibrosis and hyaline membrane. (F) Numerous *Aspergillus* colonies with tissue and angio invasion

immunosuppression regimen including calcineurin inhibitors, an anti-metabolite, and steroids. They were also administered solumedrol and basiliximab before reperfusion as part of our induction immunosuppression protocol for all patients undergoing LTx. In addition, they received antimicrobial drugs directed toward the pathogens isolated from the native lungs before transplant. All recipients underwent serial bronchoscopies to monitor anastomotic healing, to collect broncho-alveolar lavages to monitor or rule out infections, and for toileting. There was no recurrence of SARS-CoV-2 infection in allografts.

We faced certain challenges preoperatively as well as postoperatively.

The preoperative challenges were: 1. recipients were referred to the transplant center after prolonged ICU stays on mechanical ventilation, 2. pre-existing sepsis and infections and their control before LTx, 3. significant neuro-muscular weakness or critical illness neuropathy affecting both upper and lower limbs, 4. prolonged ECMO runs initiated as bridge to transplant, 5. pulmonary rehabilitation limitations on ECMO, and 6. maintaining adequate and prolonged nutritional support.

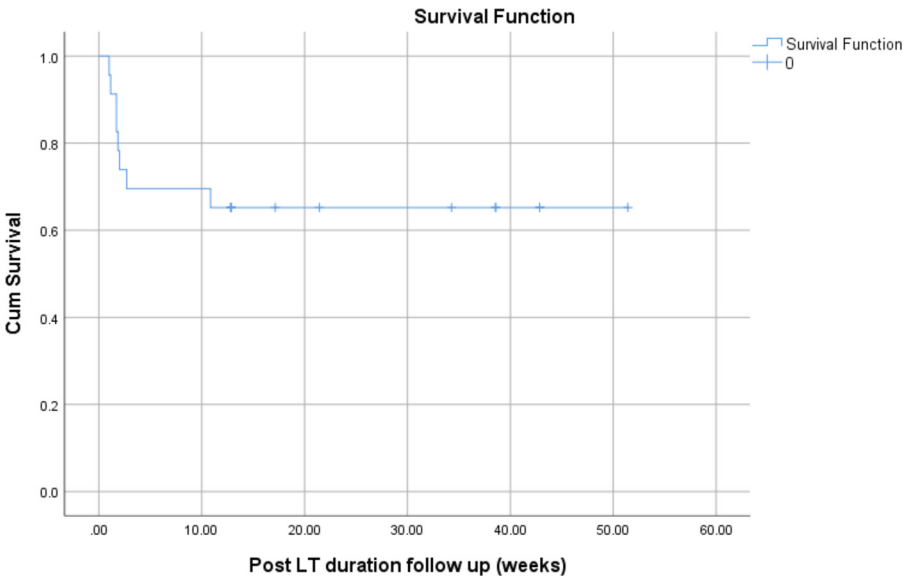


Fig. 5. Kaplan Meir curve with survival function. Cum, cumulative, LT, lung transplant

Table 4. Comparison of Demographic variables between status at final follow up (N = 23)

	Status at Final Follow-up			
Demographic Variables	Alive	Expired	χ^2/Fisher Exact	*P* value
Age group (%)				
<60 (n = 20)	14 (70)	6 (30)	1.54	.27
≥60 (n = 3)	1 (33.33)	2 (66.67)		
Sex (%)				
Male (n = 20)	13 (65)	7 (35)	0.003	1.00
Female (n = 3)	2 (66.67)	1 (33.33)		
Body mass index (%)				
Normal (n = 5)	3 (60)	2 (40)	0.619	.73
Overweight (n = 13)	8 (61.5)	5 (38.5)		
Obese (n = 5)	4 (80)	1 (20)		
Comorbidities				
Yes (n = 8) (%)	4 (50)	4 (50)	1.252	.37
No (n = 15) (%)	11 (73.33)	4 (26.67)		
Pretreatment ventilation d	52 (33,56)	47.5 (30.25,79)		.77
Total ECMO d	37 (26,52)	53.5 (19.75,76.25)		.60
Total ECMO wk	5.29 (3.71, 7.43)	7.64 (2.82, 10.89)		.60
Total ECMO (wk)				
<6 wk (n = 12) (%)	9 (75.0)	3 (25)	1.059	.30
≥6 wk (n = 11) (%)	6 (54.5)	5 (45.5)		
Explant lung weight left (g)	460 (353,586)	499.5 (345.75,587.5)		.65
Explant lung weight right (g)	541 (380,644)	590 (507.5.688)		.22
Volume (explant dimension-left)	1017.5 (825, 1275)	1079 (838.75, 1225.5)		.74
Volume (explant dimension-right)	1309 (897.75, 1584)	1606 (1158.75, 2089.05)		.16
Ischemia time left (min)	351 (300,410)	349 (275.25,425.5)		.77
Ischemia time right (min)	220 (174,287)	237.5 (152.5.333.25)		1.00
Intraop total no. of blood products	11 (9.12)	12 (11,19.5)		.055
PGD grade at 72 h (%)				
0 (n = 4)	4 (100)	0 (0)	8.437	.052
1 (n = 4)	4 (100)	0 (0)		
2 (n = 7)	2 (28.57)	5 (71.43)		
3 (n = 8)	5 (62.5)	3 (37.5)		
Hospital stay (d)	65 (47,84)	33 (25.5.85.75)		.175

ECMO, extracorporeal membrane oxygenation; intraop, intraoperative; PGD, primary graft dysfunction.

The intraoperative challenges were: 1. as most of the recipients were on ECMO support, LTx was performed on ECMO support, and all of them converted to VA ECMO from VV ECMO preoperatively; and 2. the need for multiple blood products transfusions intraoperatively.

The postoperative challenges were as follows: 1. maintaining tacrolimus levels toward the lower limit of the acceptable range in order to prevent super-added infections from an Indian perspective, 2. aggressive pulmonary rehabilitation required because of significant critical illness neuropathy, 3. tackling a variety of infections (bacterial, viral, and fungal), 4. prolonged tracheostomy care, 5. keeping a low threshold for suspecting rejections and managing them, and 6. delayed wound healing in some recipients.

We had 14 recipients with positive blood cultures, with some recipients among them showing breakthrough infections. This highlights that such phenotypes are probably at risk of multiple infections—post−viral immunosuppression, prolonged courses of steroids and/or Tocilizumab, and comorbidities like diabetes mellitus might contribute to the risk of infections.

In the study published by Bharat et al [9], authors have described their experience of LTx in such phenotypes. Various concerns regarding LTx in patients with SARS-CoV-2 or superinfecting pathogens associated with viral pneumonia in the native lung recurring in the allograft, severe vascular and pleural damage secondary to SARS-CoV-2 infection causing technical barriers to transplant, increasing time that tissues are ischemic leading to worsening of outcomes, severe deconditioning associated with prolonged mechanical ventilation, sedation, and neuromuscular blockade and malnutrition which might complicate recovery after transplant were discussed. The normal functional status of the patients before their SARS-CoV-2 −induced pneumonia would reduce the impact of these factors on recovery after LTx. They concluded that some patients with severe COVID-19 develop an irreversible fibrotic lung disease for which transplant is likely their only option for survival.

We would like to raise similar concerns of these patients developing multiple nosocomial complications, neuromuscular deconditioning, and malnutrition due to their complicated medical course, which may be an impediment to transplantation in patients. We found these factors that affected postoperative recovery period for a select few recipients, specifically those with >60 years of age, a body mass index of more than 30, a donor-recipient lung size mismatch leading to anatomic volume reduction in some, prolonged ischemia times, acute kidney injury postoperatively, and so on. More studies are required to analyze the above risk factors in these post-COVID phenotypes going for LTx.

Barbaro et al [10] in their study has reinforced above findings regarding risk factors. Novel findings in this study include determination of independent associations between mortality and risk factors for ECMO-supported patients with COVID-19. Identified risk factors were age, immunocompromised state, chronic respiratory disease, pre-ECMO cardiac arrest, degree of hypoxaemia, presence of acute kidney injury, and use of ECMO for temporary circulatory support (VA ECMO support vs VV ECMO support).

Cypel and Keshavjee [7] have highlighted determinants of LTx. The challenges in selection of candidates for LTx in such situations also has been highlighted by Domjan et al [11].

Extrapolating the above recommendations in patients post-COVID would require some deviations.

We propose that candidacy for LTx in such patients should be decided by the following factors (apart from those mentioned above):

1. Duration of ECMO days with high sequential organ failure assessment scores, specifically from Asian countries where financial constraints and risk of infections on ECMO support could be higher;
2. Preoperative infection status, comprehensively evaluating bacterial, fungal, and viral etiologies beforehand;
3. Assessing neuromuscular deconditioning, using less sedation and neuro-muscular blockades preoperatively;
4. Limitations in pretransplant evaluations specifically for patients on ECMO and ventilatory support referred for LTx;
5. Multiorgan derangement preoperatively on ECMO support while awaiting organ allocation.

Several studies and reviews have been published describing histopathological features in SARS-Cov-2 infected and damaged lungs. Studies by Polak et al [12], Chen et al [13], and Luo et al [14] confirm our histopathological findings of explanted lungs.

Key points elicited for LTx by Yu et al [15], in post-COVID patients are:

1. Confirmed irreversibility of refractory respiratory failure despite maximal medical support;
2. Confirmed positive-turned-negative virology status by performing consecutive nucleic acid tests with samples derived from multiple sites;
3. Confirmed absence of other organ system dysfunction that could contraindicate LTx. LTx was regarded as an urgently needed salvage therapy after full evaluation of the pathologic condition of the patients;
4. Robust rehabilitation procedures and early mobilization for post−COVID-19 patients provided enormous strength to pursue a good quality of life;
5. Head covers with positive pressure are necessary for surgeons, nurses, anesthesiologists, and cardiopulmonary physicians; head covers will help surgeons keep their field of view clear without fogging of eye protectors;
6. Considering the physical demands and challenges for surgeons in full protective clothing, an intraprocedure rotation plan is necessary to guarantee optimal performance during surgery.

Understanding the above key factors is crucial for successful outcomes post-LTx. We propose additional points:

1. Induction immunosuppression should be used in all such recipients as they have higher risk of sensitization

preoperatively, specifically on ECMO support due to need of multiple blood products transfusions,
2. Better donor to recipient lung size match to reduce risk of PGD,
3. Lesser ischemia times,
4. Lower steroid maintenance dose in view of neuromuscular deconditioning and critical illness neuropathy.
5. Double LTx, aggressive pulmonary rehab both preoperatively and postoperatively.

Our findings, observations and recommendations have found some similarity in the recent article published by Bharat et al [16]. The authors have elaborated in-detail about criteria for the selection of post−COVID-19 LTx patients. Some criteria, like duration on ECMO support, need for aggressive pulmonary rehabilitation in ICUs preoperation, and optimum nutritional support should be stressed and relevant for recipients from Asian countries.

Reis et al [17], in a Brazilian study of 3 post-COVID LTx recipients, has also shown that LTx is feasible among these complex patients. Survival over the first 30 days was 100%, favoring surgical feasibility. Nevertheless, these were critically ill patients.

Recently, King et al [18] in their review article have highlighted their approach to LTx for COVID-related ARDS or post-COVID fibrosis. Our study also had a similar approach in deciding candidacy for LTx in such patients to find the transplant "sweet spot" as mentioned in article. Centers involved in the above review article don't represent Asian settings and their inherent challenges. It is imperative to have more work coming from Asian countries like India, China, and Japan to understand critical areas regarding candidacy as 1. ECMO waiting time till listing such phenotype, 2. "waves of infections" while on ECMO and preserving candidacy for LTx, 3. long-term outcomes posttransplant and relation to acute (acute cellular rejection or antibody-mediated rejection) or Chronic Rejections.

Strengths and Limitations

This study's findings are from a single center with a small sample size to draw meaningful insights into factors associated with outcomes and generalize the findings. Another key limitation was the data analyzed were from short-term follow-ups. Considering all the outcomes reported are major and objective in nature, the possibility of bias is very minimal. Considering the extremely low sample sizes of other published studies, the present study presenting the profile and outcomes of 23 patients undergoing double lung transplantation can be considered as highly useful and as a natural progression of evidence on the subject. The presentation of outcome data and factors associated with them was another key strength of this study. Though the inferential statistics are not scientifically robust, they will aid in formulation of research hypothesis for subsequent large-scale studies. Additionally, we could also provide meaningful insights into various aspects, including patient selection, postoperative need for robust pulmonary Rehabilitation, and absence of rejections early on in surveillance biopsies based on our experience with a reasonable volume of such patients, specifically from Asian clinical settings. This study might help better understanding of recipient selection, timely referrals, and postoperative challenges coming from developing countries with high case numbers. It would be interesting to see and compare results with centers from developed countries with a high volume of COVID LTx.

CONCLUSIONS

Performing LTx in patients post-COVID with ESLD comes with unique challenges. Selecting the right candidates is a challenge in some clinical scenarios. More studies of LTx are required in patients post-COVID with ESLD to understand long-term follow-up, outcomes, and the risk of chronic lung allograft dysfunction.

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