VIA MEDICA

REVIEW ARTICLE

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SARS-CoV-2 and lung transplantation. What do we know?

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ABSTRACT

Introduction: In 2019, new Coronavirus (SARS-CoV-2) has spread around the globe. The virus can replicate in the cells of the lower respiratory tract, causing pneumonia, oedema and hypoxia. In some patients, the disease will progress to acute respiratory distress syndrome (ARDS) which is a life-threatening condition. Lung transplantation (LuTx) might be the only rescue therapy for severe respiratory failure. Additionally, little is known about the impact of SARS-CoV-2 on lung transplant recipients. The purpose of this systematic review is to present current knowledge about lung transplantation as a treatment method for ARDS associated with COVID-19 infection and to summarize information regarding the management of COVID infection in lung transplant recipients.

Materials and methods: Literature search through different databases was conducted. Only case reports and case series were included.

Results: Out of 525 initial results, 16 studies were included in this systematic review. 7 articles presented patients with LuTx as a treatment option for ARDS and 9 presented management of lung recipients infected with COVID-19. A total of 37 patients were included in this systematic review.

Discussion: The course of reviewed patients with SARS-CoV-2 infection was similar and lung transplantation should be considered as a treatment of last chance when extracorporeal life support cannot be withdrawn. Further research is still required to assess the impact of new coronavirus on graft function in lung transplant recipients. Currently, the treatment strategy involves immunosuppression modification and supplemental oxygen therapy. However, some patients do not present clinical symptoms.

Key words: lung transplantation, coronavirus, COVID-19, ARDS

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Introduction

Since December 2019, medical centers around the world have been struggling with the Covid-19 pandemic. The virus mainly affects the respiratory system; some patients may progress to acute respiratory distress syndrome (ARDS). Advanced age and comorbidities are considered as risk factors for severe disease. In 97% of the patients undergoing acute Covid-19 infection pathological changes in the chest are seen on CT images [1]. In case of irreversible and serious lung parenchyma damage, lung transplantation (LuTx) might be necessary to restore respiratory efficiency. LuTx is a treatment of the last chance performed in patients with end-stage lung diseases when conventional treatment does not provide improvement. According to the International Society of Heart and Lung Transplantation (ISHLT), LuTx might be considered in patients with a 2-year mortality rate greater than 50% without transplant. Furthermore, a 5-year survival rate > 80% is required. In addition, this challenging surgery is associated with a long list of contraindications. For instance, the recent history of malignancy or dysfunction of another organ. Age over 65 years is a relative contraindication [2]. While LuTx is a life-saving surgery for patients with respiratory diseases, severe Covid-19 is associated with higher age and comorbidities that might prevent from becoming a potential candidate for transplantation [3]. There is a limited number of reports of LuTx performed due to Covid-related ARDS in the literature. Furthermore, the current SARS-CoV-2 pandemic represents a significant risk for lung transplant recipients. Little is known about the potential impact of the virus on graft function. Therefore, this systematic review presents

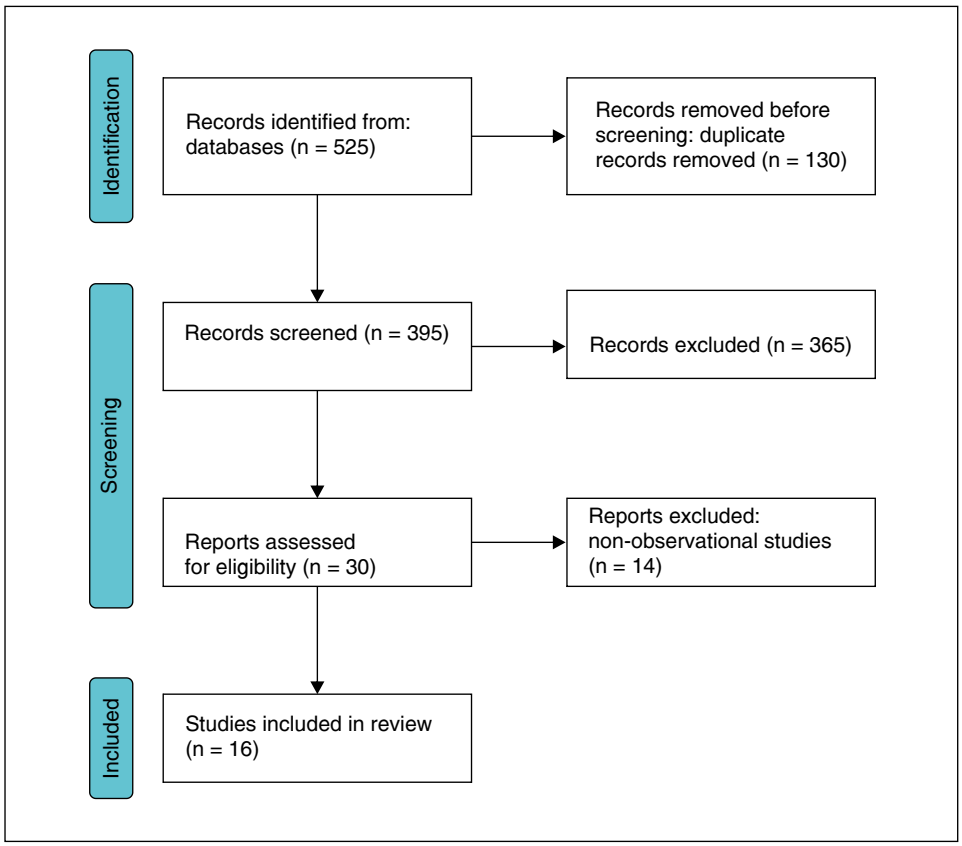

Figure 1. Flow diagram illustrating selection of the articles included in the systematic review

patients who underwent LuTx due to Covid-19 related ARDS and lung transplant recipients with postoperative Covid-19 infection. This systematic review aims to summarize current knowledge about SARS-CoV-2 infection that may lead to lung transplantation. Clinical features and management of patients progressed to ARDS are presented. Secondly, management of lung transplant recipients infected with Covid-19 is depicted as it may be beneficial for the development of future guidelines of postoperative care.

Materials and methods

This systematic review was conducted using PRISMA protocol (Preferred reporting items for systematic reviews and meta-analyses) [4]. Literature search through PubMed/Medline and Embase was performed. Flowchart representing search strategy is depicted in Figure 1. Phrases used for searching included: lung transplantation for Covid-19; lung transplant recipients Covid-19. Only case reports and case series written in English describing patients who underwent LuTx due to SARS-CoV-2 or lung transplant recipients with Covid-19 infection were included. 525 studies were identified after an initial search through databases. 395 studies' titles and abstracts were screened. After exclusion of non-observational studies and articles about transplantation of organs other than lungs, 30 studies remained for full-text assessment. 16 case reports and case series were ultimately included in this systematic review. Two reviewers independently screened titles and abstracts of studies chosen after primary search. Data was extracted manually from included studies. The second evaluation was performed in case of uncertainty. Characteristics (name of the first author, publication year, country, study design and infection status) of reviewed articles are presented in Table 1.

Results

7 articles presenting 13 cases of patients with ARDS were reviewed (Tab. 2). Mean age of presented patients was 54 ± 8,7 years. Presented cases included 4 females and 9 males. Some of the patients suffered from comorbidities like hypertension, diabetes or psoriasis, which might have contributed to the severe course of Covid-19. In all of the presented patients Extracorporeal

Table 1. Characteristics of articled included in the systematic review

Author	Year	Country	Study / number of patients	COVID-19 infection
Han W. [5]	2020	China	Case series / 2	Before LuTx
Lang C. [6]	2020	Austria	Case report	Before LuTx
Chen J.Y. [7]	2020	China	Case series / 3	Before LuTx
Bharat A. [8]	2020	USA	Case series / 3	Before LuTx
Chen Y. [9]	2021	China	Case report	Before LuTx
Hu C. [10]	2021	China	Case report	Before LuTx
Croci G.A. [11]	2021	Italy	Case series / 2	Before LuTx
Aigner C. [12]	2020	Germany	Case report	After LuTx
Koczulla R.A. [13]	2020	Germany	Case series / 2	After LuTx
Morlacchi L.C. [14]	2020	Italy	Case series / 4	After LuTx
Athanazio R.A. [15]	2020	Brazil	Case report	After LuTx
Cozzi E. [16]	2020	Italy	Case series / 2	After LuTx
Raëth J. [17]	2020	France	Case report	After LuTx
Renaud-Picard B. [18]	2020	France	Case report	After LuTx
Verleden G.M. [19]	2020	Belgium	Case series / 10	After LuTx
Desmazes-Dufeu N. [20]	2021	France	Case series / 2	After LuTx

LuTx — lung transplantation

Membrane Oxygenation (ECMO) was applied due to respiratory failure. To support circulation for weeks, veno-venous ECMO had to be applied (bridge to LuTx), while veno-arterious ECMO was required intraoperatively. In 9 of reviewed cases, pulmonary artery hypertension (PAH) was observed. In the presented cases, mean time from Covid-19 confirmation to LuTx was 53,6 ± 14 days which shows how rapid the disease progression might be. Pathological examinations of resected lungs were similar. The mixture of fibrotic and necrotizing tissues was observed. Extensive consolidation and micro-thrombosis were found as well. In the majority of reviewed cases, large improvement was observed postoperatively. Extracorporeal life support has been withdrawn successfully days or weeks after LuTx while it was impossible prior to surgery. Lung function was mostly restored, and saturation was increased. Furthermore, patients regained independence in everyday activities. One death on postoperative day 1 was observed.

In addition, 9 case reports and case series with a total of 24 lung transplant recipients infected with COVID-19 were included (Tab. 3). Mean age of the patients was 51.5 ± 6.7 years. The mean time from LuTx to Covid-19 infection was 63.9 ± 25.7 months and the causes of LuTx included Chronic Obstructive Pulmonary Disease (COPD), Cystic Fibrosis (CF), non-specific interstitial pneumonia, pulmonary fibrosis, pulmonary hypertension, lymphangioleiomyomatosis and bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. Reviewed patients presented diversified symptoms. These included mild cold symptoms like fever, cough in some patients while others suffered from progressive dyspnea, malaise, hypoxia or thrombosis. In 13 patients ground-glass opacities in chest CT were observed. In 15 cases immunosuppression therapy was changed; cycle cell therapy was stopped (mycophenolate mofetil). In the vast majority of reviewed cases, antibacterial therapy was introduced, for instance, azithromycin, meropenem. In some patients, low molecular weight heparin was introduced. 3 patients had died (1 from multiorgan failure, 1 from graft injury caused by Covid-19 and bacterial infection, 1 from the deteriorated gas exchange).

Discussion

Coronaviruses are known for infections of the upper respiratory tract which cause mild symptoms. However, there are three viruses that replicate in the cells of the lower respiratory tract: Middle East respiratory syndrome coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and SARS-

Table 2. Reviewed case reports of patients with SARS-CoV-2 related ARDS

Author	Patient age	Sex	Comorbidities	Lung function/radiological images prior to LuTx	ECMO support before LuTx (days)	Pathological examination	Postoperative course	Time from COVID confirmation to LuTx (days)
Han W. [5]	66	Female	–	Oxygenation index < 60 mmHg X-ray manifestations: "white lung" Pulmonary artery systolic pressure 80 mmHg	–	Uneven surface, entirely consolidated in cross-section	Acute rejection treated with steroids ECMO successfully removed on POD 5	–
	70	Male	Hypertension Diabetes Psoriasis	Chest radiographs: Large blurry images of both lungs	10	Extensive consolidations	ECMO withdrawn on POD 2	35
Lang C. [6]	44	Female	Psoriatic arthritis	Gradual worsening of respiratory function	45	Large zones of necrosis Massive alveolar damage Remnants of widespread thromboembolism throughout all lobes	ECMO removed on POD 3 Quick recovery	58
Chen J.Y. [7]	66	Male	Hypertension	Oxygen Index: 60 Pulmonary Artery Pressure: 52	15	Congestive and hemorrhagic necrosis Extensive pulmonary interstitial fibrosis Micro-thrombosis	Death on POD 1	35
	58	Male	HBV infection	Oxygen Index: 104 Pulmonary Artery Pressure: 48	7	Congestive and hemorrhagic necrosis Extensive pulmonary interstitial fibrosis Intravascular organized thrombosis	ECMO removed on POD 2	33
	73	Male	Diabetes Chronic Kidney Disease Coronary Heart Disease Atrial Fibrillation COPD	Oxygen Index: 114 Pulmonary Artery Pressure: 40	19	–	ECMO removed on POD 2	37

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Table 2 cont. Reviewed case reports of patients with SARS-CoV-2 related ARDS

Author	Patient age	Sex	Comorbidities	Lung function/radiological images prior to LuTx	ECMO support before LuTx (days)	Pathological examination	Postoperative course	Time from COVID confirmation to LuTx (days)
Bharat A. [8]	28	Female	Neuromyelitis optica	Gradual decrease in PaO2 despite mechanical ventilation Right-sided pneumothorax Serratia marcescens pneumonia with left lower lobe necrosis Pulmonary pressure elevation (71/49 mmHg)	–	Severe dense vascular adhesions diffuse alveolar hemorrhage	Separated form VV – ECMO and MV in two weeks Discharged home 4 weeks after LuTx	–
	62	Male	Hypertension	Recurrent pneumonia caused by *Pseudomona aeruginosa*, hemothorax and empyema requiring thoracotomy and lung decortication	100	Loss of normal mediastinal tissue planes; extensive pleuritis diffuse alveolar hemorrhage Lung necrosis secondary to larger thrombi	Four months after LuTx: saturation 97% while breathing room air, independence in common activities	–
	43	Male	Diabetes	Progressive lung fibrosis Severe pulmonary hypertension with right ventricular dysfunction	–	Diffuse alveolar hemorrhage	Three months after LuTx: saturation 95% while breathing room air	90
Chen Y. [9]	66	Female	–	Pulmonary artery pressure: 80 mmHg Respiratory failure with consolidation of the lung seen on X-ray Saturation 74%	14	–	ECMO removed on POD 5 Gradual improvement	–
Hu C. [10]	59	Male	Hepatitis B	Respiratory failure and irreversible lung injury Chest CT: bilateral, ground-glass opacities with consolidations.	–	–	ECMO removed on POD 2 Chest X-ray: significantly improved lung imaging	–
Croci G. A. [11]	18	Male	–	Bilateral pneumothorax Pneumatocele Severe pulmonary hypertension Pulmonary infections	55	Hepatization foci of hemorrhage and consolidation	–	71
	48	Male	–	Severe pulmonary hypertension Right ventricular failure Pulmonary infections	54	Bronchiectasis small peripheral foci of hemorrhage and emphysema	–	70

ECMO — extracorporeal membrane oxygenation; POD — postoperative day; COPD — chronic obstructive pulmonary disease

Table 3. Summary of the case reports and case series findings

Variable		Number of patients/ /number of studies
Male		10/6
Female		13/6
Age > 65 years		6/4
Single lung transplantation		2/2
Bilateral lung transplantation		19/7
Cause of LuTx	Chronic obstructive pulmonary disease	8/3
	Cystic fibrosis	7/6
	Bronchiectasis	2/1
	Non-specific interstitial pneumonia	1/1
	Pulmonary fibrosis	1/1
	Pulmonary hypertension	2/2
	Pulmonary lymphangioleiomyomatosis	1/1
	Bronchiolitis obliterans after hematopoietic stem cell transplantation	1/1
Symptomatic		20/7
Asymptomatic		3/3
Ground-Glass opacities in CT		14/7
CPAP/oxygen therapy/mechanical ventilation		13/6
Immunosuppression modification		16/5
Antibacterial therapy		21/7
LMWH		5/3
Death		3/3

CPAP — continuous positive airway pressure; LMWH — low molecular weight heparin

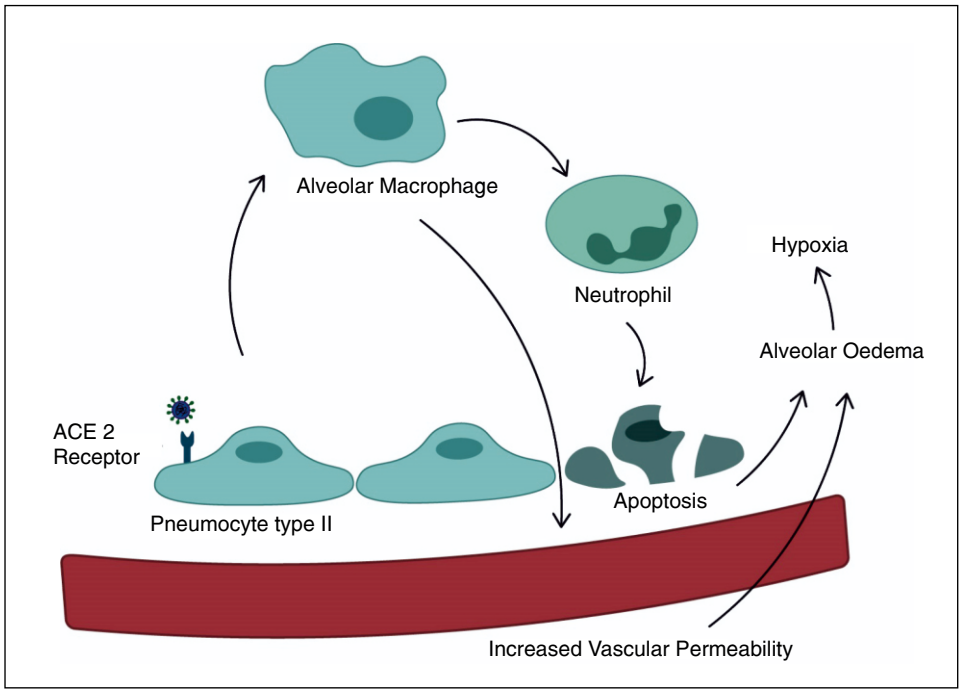

Figure 2. COVID-19 immunopathology

CoV2 [21]. It is considered that the SARS-CoV-2 virus attacks all cells that express angiotensin-converting enzyme 2 receptor (ACE2) which is an entry receptor. Consequently, as the virus replicates its genome, the hosts immunology system is activated and proinflammatory cytokines are secreted. Alveolar macrophages stimulate vascular permeability and recruit neutrophils. Degranulation of these cells is responsible for pneumocytes and endothelial cells damage. Thus, these processes lead to alveolar oedema and hypoxia and are associated with the progressive development of ARDS (Fig. 2) [22]. Chronic inflammation and unsuccessful regeneration contribute to the development of pulmonary fibrosis, leading to damage of lung architecture. It is suggested that recruitment of myofibroblasts and alveolar epithelial damage are causes of most lung fibrosis processes [23]. In some of the reviewed cases, pathological examination revealed thrombosis of pulmonary vessels. Dysfunction of coagulation appears to be common in the course of Covid-19 infection. Vascular enlargement, which can be observed in chest CT, is frequently seen in Covid-19 patients while it is rarely reported in typical ARDS. Furthermore, Covid-19 related ARDS is associated with increased mortality rates compared to typical ARDS [24]. Respiratory failure due to ARDS is a life-threatening condition. In such cases, extracorporeal membrane oxygenation is a rescue therapy, and it was introduced in all of reviewed ARDS cases. Cannulation strategy for acute respiratory distress syndrome is a veno-venous ECMO, as it might support a patient for weeks. Furthermore, early use of VV-ECMO may reduce pulmonary inflammation and lower respiratory-driven pressure. Therefore, with its lung-protective mechanism, it is an accepted treatment for patients with ARDS [25]. However, if trials of ECMO removal are unsuccessful and patients condition does not seem to improve, lung transplantation might be the rescue therapy. However, during LuTx, veno-arterious ECMO should be applied, as VV-ECMO does not support cardiac function. In some patients, pulmonary artery hypertension (PAH) was observed. It is diagnosed when mean pulmonary arterial pressure is greater than 25 mmHg. PAH is associated with an increased risk of severe course of Covid and higher mortality rates [26].

In reviewed articles, the mean time of ECMO support prior to LuTx was 35,4 ± 19 days. Mean time from COVID confirmation to LuTx was 53,6 ± 14 days. In analysis performed by Chen J. et al. out of 249 patients, 8 (3,2%) progressed to ARDS in 4.8 ± 2.4 days after the beginning of symptoms [27] which shows how rapid the disease progression to irreversible pulmonary damage may be.

It is unclear how SARS-CoV-2 infection affects lung transplant recipients and graft function. In reviewed articles, the course of infection varied among patients. In the majority of reviewed articles, patients presented fever, cough, dyspnea or hypoxia. However, three patients underwent Covid-19 infection without clinical symptoms. A total of 13 patients required supplemental oxygen therapy, mechanical ventilation or continuous positive airway pressure (CPAP). Together with noninvasive ventilation, CPAP is introduced in patients with hypoxemic respiratory failure as a result of pulmonary oedema. Due to the lack of randomized control trials, there are no recommendations for using CPAP in viral infections. According to a retrospective review performed by Brusasco C. et al. 64 patients were supported with CPAP due to Covid-19 respiratory failure. Criteria for CPAP application were: $PaO_2/FIO_2 < 200$, $PaO_2 < 60$mmHg, breathing frequency > 30 min and dyspnea at rest. The majority of patients recovered after the use of CPAP (n = 53) and were discharged from the hospital within 28 days [28]. In large number of patients chest CT revealed ground-glass opacities (GGOs). Chest CT is a significant tool in COVID diagnosis due to its high sensitivity. Replicating virus in alveolar epithelium and damage of epithelial surface (leakage) manifest as GGOs. Other changes involve vascular enlargement, consolidation and bronchial wall thickening. These changes usually occur bilaterally [29]. According to a systematic review performed by Salehi S. et. al GGOs may be observed in the early stage of infection (1–2 weeks after exposure). Furthermore, these changes may be observed despite negative COVID-19 PCR results [30]. Thus, chest CT could be beneficial to identify the early stage of coronavirus infection in lung transplant recipients. Immunosuppression therapy for lung recipients consists of three elements: calcineurin inhibitors (tacrolimus), cycle cell inhibitors (mycophenolate mofetil) and corticosteroids. In reviewed cases, mycophenolate was reduced or stopped during infection. This approach was also undertaken by Pereira M.R. et al. in solid organ transplant recipients with Covid-19 [31]. Elevation of proinflammatory cytokines (IL-6, TNF) was observed in patients with severe course of SARS-CoV infection. Those are involved in abnormal clot formation leading to the development of thrombosis. Thus, low molecular weight heparin (LMWH) should be considered to prevent deep vein thrombosis or clot formation in pulmonary vessels. Among reviewed cases, 5 patients were treated with LMWH [32]. According to analysis performed by Coll E. et al., who reviewed 778 solid organ and haemopoietic stem cell transplant recipients, lung transplant recipients (n = 54) had a significantly higher risk of death (OR: 2.5 95% CI: 1.4–4.6). Furthermore, the course of infection was more aggressive compared to recipients of other organs which may be related to more potent immunosuppression and poorer respiratory reserve [33]. According to a report written by

Messika J et. al, among 35 lung recipients, 31 (88,6%) required hospitalization due to Covid-19 infection. The presentation was mostly severe, while 5 patients died due to Covid-19 infection [34]. The early phase of the Covid-19 pandemic reduced the number of lung transplantations performed [35]. Consequently, more patients are on the waiting list and more deaths among those patients has occurred [36]. This systematic review should be considered with several limitations. Firstly, despite a comprehensive search of available studies, some upcoming articles could have been missed due to evolving nature of Covid-19. Secondly, some cases of lung transplant recipients could have been described in studies summarizing recipients of other organs as well, not meeting the inclusion criteria for this review. These factors might be responsible for introducing a bias.

Conclusions

The global pandemic proved to be a critical challenge for healthcare systems and physicians. Lung damage caused by SARS-CoV-2 may be thorough and irreversible. Supplemental oxygen therapy or ventilation is used to support patients in worsening conditions.

However, if the deterioration of lung function progresses, extracorporeal membrane oxygenation might be a rescue therapy. Failure in ECMO withdrawal indicates that lung transplantation is required. As seen in reviewed cases, LuTx provided an improvement and ECMO could be withdrawn few days after the surgery. Therefore, Covid-19 related ARDS might be treated, and mortality rates lowered. However, with limited access to extracorporeal circulatory support devices and an increasing number of Covid-19 patients with ARDS due to ongoing pandemic, this treatment strategy may be approachable only in certain patients. Performing LuTx in patients with severe ARDS associated with Covid-19 is extremely challenging as there are not any official guidelines. Furthermore, the surgery itself is a very invasive treatment. Additional use of extracorporeal life support increases the risk of other serious complications like acute kidney injury, bleeding or thromboembolic complications. Coronavirus pandemic introduced obstacles that have not been previously encountered. For instance, testing donor's lungs for Covid-19; providing surgical facilities with adequate protection level or wearing virus protection suits by the surgical team. In addition, little is known about the potential impact of Covid-19 on lung transplant recipients and further research is required to develop adequate guidelines of postoperative care. We strongly believe that this review may be beneficial as it promotes lung transplantation as a treatment of the last chance in case of patients who progressed to ARDS due to Covid-19 infection. Furthermore, a summary of treatment methods and management of infected lung transplant recipients may be helpful in developing future guidelines.

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