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Research Article

Lung Transplant Recipients with COVID-19-infection Management: Systematic Review and Meta-analysis

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Abstract

A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including ScienceDirect, PubMed, Scopus, MedRxiv COVID-19 or SARS-CoV-2, ISI Web of Science, and websites of the news. The search was applied to the articles that were published between year 2004 and half year 2021. With strict literature search and screening processes, it yielded 26 articles (2004 = 1; 2009 = 1; 2019 = 1, 2020 = 15 and half year 2021 = 8 articles) from 405 articles of initial literature database (1998-half year 2021). Currently, the Vienna Lung Transplantation Program, plays a leading role in an international consortium comprising transplantation experts from Asia, Europe, and USA. A previous cohort study among 90 solid-organ-transplant (SOT) recipients with COVID-19 infection, included 17 lung-transplant recipients (LTRs) and kidney-transplant recipients demonstrated overall mortality of about 24%. In patients awaiting for transplantation who are unlikely to receive an organ donor within 2-3 weeks, the ISHLT recommends COVID-19 vaccination, whereas the guidelines recommend a waiting period of one month post-transplantation and 3 - 6 months post-administration of B- or T-cell depleting agents and a protocol recommended 90 days for both post-transplantation and 3 - 6 months post-administration of B- or T-cell depleting agents. For the application of this issue, we now have some experience and insight for COVID-19-infected LTRs. We look forward to getting the optimal timing of COVID-19 vaccination adjustment of immunosuppression in LTRs, whereas the investigations of the T-cell response and additional COVID-19-vaccine doses are ongoing. In conclusion, Long-term outcomes of lung transplantation in severe COVID-19 patients are still to be investigated. National and international regulatory transplantation professional bodies should track the transplant-COVID-19 patient for establishing the standard guidelines.

Keywords: COVID-19; Immunization; Immunocompromization; Lung; Outcome; Risk Factor; SARS-CoV-2; Transplantation; Vaccination

Abbreviations

CLAD: Chronic Lung Allograft Dysfunction; COVID-19: Coronavirus Disease 2019; CNIs: Calcineurin Inhibitors; CRP: C-Reactive Protein; CRS: Cytokine Release Syndrome; FiO_2: Fraction of inspired Oxygen; FEV_1: Forced-Expiratory Volume in one second; ICU: Intensive Care Unit; IL: Interleukin; ISHLT: International Society of Heart

and Lung Transplantation; LTRs: Lung-Transplant Recipients; m TOR: Mammalian Target of Rapamycin Inhibitor; PaO_2: Partial pressure of Oxygen; RT-PCR: Reverse-Transcriptase Polymerase Chain Reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; SOT: Solid-Organ Transplantation; SpO_2: Blood Oxygen Saturation; VTE: Venous Thromboembolic Events

Introduction

A previous study between May 1, 2020 and September 30, 2020 in 12 patients with COVID-19-related ARDS underwent bilateral lung transplantation at six high-volume transplant centers in 4 countries (USA-eight recipients at three centers, Italy-two recipients at one center, Austria-one recipient, and India-one recipient) [1]. Nine of the 12 recipients were male with the median age of 48 years (IQR: 41-51) [1]. Severe lung damage that did not improve despite extracorporeal membrane oxygenation and prolonged mechanical ventilation [1]. Increased intraoperative transfusion requirements, hilar lymphadenopathy, and severe pleural adhesions were the technically lung transplant procedure challenging [1]. Extensive, ongoing acute lung injury with lung fibrosis was the demonstrated in the explanted lungs [1] . No recurrence of SARS-CoV-2 infection or pathology in the lung allografts was demonstrated and all 12 patients could be weaned off extracorporeal support with short-term survival similar to that of transplant recipients without COVID-19 [1]. The characteristics of the lung donors in this study 8 males (67%), 4 females (33%), median age of 34 years (29 - 43), 173 (170 - 179) cm. of height, 84 (76 - 92) kg of weight, 6.1 (5.1 - 7.2) liters of the predicted total lung capacity, 5 (42%) with having smoking history (current or past smoker), 1 (8%) of subarachnoid bleeding cause of death, 6 (50%) traumatic brain injury cause of death, 3 (25%) drug overdose cause of death, 1 (8%) of intracerebral bleeding cause of death, 1 (8%) ischemic brain injury cause of death, 7 (58%) of normal chest roentgenogram, 5 (42%) of abnormal chest roentgenogram, 84 (66 - 105) hours of the median intubation time, 417 (362 - 489) of the PaO_2/FiO_2 at the time of offer, 39 (35 - 45) mmHg of $PaCO_2$ at the time of offer, 9 (75%) of normal bronchoscopy, 5 (25%) of abnormal bronchoscopy, 3 (25%) of ideal type of lung donor, 9 (75%) of marginal type of lung donor and 5 (3 - 7) of median Oto score [1]. Due to uncertainty of the duration of SARS-CoV-2 (COVID-19) infection in the lungs of patients with severe disease, the major concern was ongoing SARS-CoV-2 (COVID-19) infection at the time of lung transplantation and feasible reinfection of the lung allograft [2]. Several recent studies indicated rarely detecting replicating virus more than 10 days after SARS-CoV-2 (COVID-19) infection [3-5].

Currently, the Vienna Lung Transplantation Program, plays a leading role in an international consortium comprising transplantation experts from Asia, Europe, and USA [6]. They established the medical guidelines for the world criteria for potential transplantation as the following: 1) exhaustion of all conservative therapeutic options, 2) no recovery of the COVID-19-related-damaged lungs despite at least four weeks of ventilation/ECMO, 3) evidence of irreversible and advanced lung damage in several consecutive CT scans, 4) age below 65, and 5) no relevant comorbidities [6]. Additionally, lung transplant candidates must be in good physical condition and have a good chance of complete physical rehabilitation after transplantation [6].

Objectives of the Study

The objectives of the study is to review the available evidence on management on lung-transplant recipients with COVID-19 infection and current recommendation on the screening of potential-organ donors and recipients and COVID-19 vaccination both on the waitlist and after lung transplantation.

Methods of the Study

Search strategy and inclusion criteria

A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including ScienceDirect, PubMed, Scopus, MedRxiv COVID-19 or SARS-CoV-2, ISI Web of Science, and websites of the news. The search was applied to the articles that were published between year 2004 and half year 2021. Our first involved performing searches of article abstract/keywords/title using strings of [("lung transplant" or "lung transplantation" or "organ transplantation", "SARS-CoV-2" or "COVID-19", "risk factor", "outcome", "lung" or "pulmonary", "immunization", and "COVID-19 vaccination")]. After a first approach of search, published articles focusing on lung transplantation in COVID-19 (SARS-CoV-2)-infected patients were retained and the information on risk factors, outcomes, COVID-19 vaccination, and management was extracted for having a crude knowledge involving their themes. Another round of publication search was conducted for adding the missing published articles that were not identified by the first round.

All keywords combinations from "lung transplant" or "lung transplantation" or "organ transplantation", "SARS-CoV-2" or "COVID-19", "risk factor", "outcome", "lung" or "pulmonary", "immunization", and "COVID-19 vaccination" to bind the population of cases under consideration. Search string for disease groups includes ["lung transplant" or "lung transplantation" or "organ transplantation", "SARS-CoV-2" or "COVID-19", "risk factor", "outcome", "lung" or "pulmonary", "immunization", and "COVID-19 vaccination"]. The initial literature databases were further manually screened with the following rules: 1) non-COVID-19- and non-lung transplantation-related articles were excluded; 2) articles that did not report risk factors or outcomes or management related to COVID-19 or SARS-CoV-2 infection in lung transplantation were not considered, such as commentary articles, or editorial; 3) non-peer reviewed articles were not considered to be of a scholarly trustworthy validity; and 4) duplicated and non-English articles were removed. The articles were carefully selected to guarantee the literature quality, which is a trade-off for quantity.

Results

With strict literature search and screening processes, it yielded 26 articles (2004 = 1; 2009 = 1; 2019 = 1, 2020 = 15 and half year 2021 = 8 articles) from 405 articles of initial literature database (1998-half year 2021). Needed article information was extracted from each article by: 1) direct information including journal (research article, review article, meeting abstract, conference abstract, correspondence, author index, editorial board meeting abstract, discussion), book chapter, title, authors, abstract, full text documents of candidate studies, websites of the news, publishing year; 2) study year; 3) research (study) method used; 4) types of organ transplantation studied; 5) types of management studied; and 6) the conclusions made about the impacts on lung transplant recipients, including COVID-19-infected patients with waiting lung transplantation.

Outcome in management of covid-19-infected patients with lung transplantation

A previous cohort study among 90 solid-organ-transplant (SOT) recipients with COVID-19 infection, included 17 lung-transplant recipients (LTRs) and kidney-transplant recipients demonstrated overall mortality of about 24% [7]. Several risk factors for poor outcomes in LTRs with COVID-19 infection [8-10] are listed in table 1.

Risk Factors for Poor Outcomes in Lung Transplantation for COVID-19 Patients	Reference
Lower baseline forced-expiratory volume in one second (FEV_1)	[8]
New or worsening respiratory failure requiring high-flow oxygen	[8]
Non-invasive ventilation or intubation	[8,9]
Presence of lung parenchymal opacities on hospitalization-chest radiograph	[8]
Longer time between symptom onset to beginning the COVID-19 anti-viral therapy	[8]
COVID-19-related pneumonia upon ICU admission	[10]

Table 1: Demonstrating risk factors for poor outcomes in lung transplantation for COVID-19 Patients.

Discussion

In addition to acute allograft rejection, the differential diagnosis of COVID-19-related pneumonia in LTRs includes aspiration pneumonia, acute lung injury, and potential opportunistic infectious pneumonia [11]. Outpatient observation is recommended when COVID-19-infected LTRs present with absence of gastrointestinal symptoms, such as nausea and vomiting, no severe disease symptoms, such as persistent fever (more than 38° C), confusion, hypotension, lethargy, etc., severe cough, absent or minimal dyspnea, pleuritic chest pain, or lung wheezing [12]. The conventionally diagnostic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies contributes to the risk of COVID-19 exposure to the healthcare providers [12]. A previous study demonstrated that COVID-19-infected LTRs could develop specific IgG antibody against SARS-CoV-2 (COVID-19) [13]. About 50% of them who died had worse FEV_1 and were diagnosed chronic lung allograft dysfunction (CLAD), compared with 25% in discharged group [13]. Higher serum levels of interleukin (IL)-6, D-dimer, lactate dehydrogenase, and ferritin and lower lymphocyte counts were found in patients with disease progression [13,14]. Computed tomography of the chest is useful for the diagnosis of pulmonary embolism, whereas bedside-Doppler ultrasonography is useful for the diagnosis of deep venous thrombosis and assessment of the vascular volume status and the cardiac function [12]. COVID-19-infected LTRs who do not meet the ambulatory management criteria should be COVID-19-designated-area hospitalized that is similar to

the general population [12]. The absence of cytokine release syndrome (CRS) is strongly indicated by a normal or significant reduction of IL-6 or C-reactive protein (CRP) levels [12]. The absence of bacterial superimposition is strongly indicated by a normal or downtrend of procalcitonin levels [12]. The D-dimer levels of at lease 3 µg/mL [15,16], and presence of thrombocytopenia [17] and antiphospholipid antibodies [18] are related to increased risk of venous thromboembolic events (VTE). ISHLT criteria for reactivation of lung transplantation waitlist [19] are shown in table 2.

Clinical Scenario	Criteria for Reactivation
Positive SARS-CoV-2 RT-PCR Asymptomatic	Two negative SARS-CoV-2 RT-PCR tests, 24-48 hours apart
	Asymptomatic patients with remaining positive RT-PCR more than 28 days
	Diagnosis if high risk mortality without a transplantation
	14 days since the diagnosis unless high risk mortality without a transplantation
Previous symptomatic COVID-19	Two negative SARS-CoV-2 RT-PCR tests, 24-48 hours apart
	Asymptomatic patients with remaining positive RT-PCR more than 28 days since the diagnosis if high risk mortality without a transplantation
	28 days from the onset of symptoms, can be shortened to 14-28 days if high risk mortality without a transplantation
	No other COVID-19-related organ damage
	Clinical resolution
Exposure to suspected or confirmed COVID-19 case within last 14 days	7 days post-exposure
	Two negative SARS-CoV-2 RT-PCR tests, 24-48 hours apart
	Asymptomatic
	High risk of mortality without an organ transplantation

Table 2: Demonstrating the ISHLT criteria for the reactivation of waitlisted COVID-19 patients.

In patients awaiting for transplantation who are unlikely to receive an organ donor within 2-3 weeks, the ISHLT recommends COVID-19 vaccination, whereas the guidelines recommend a waiting period of one month post-transplantation and 3-6 months post-administration of B- or T-cell depleting agents [19] and a protocol recommended 90 days for both post-transplantation and 3-6 months post-administration of B- or T-cell depleting agents [12]. In lung transplantation, the goal of immunosuppression strategy is to achieve a balance between suboptimal immunosuppression and excessive immunosuppression [20]. The ISHLT recommends azathioprine, mammalian target of rapamycin inhibitor (m TOR), or mycophenolate mofetil (MMF) in moderate to severe COVID-19 LTRs [19], whereas an institute keeps calcineurin inhibitors (CNIs) (IL-6 inhibitors) at the baseline dose [12]. Sarilumab or tocilizumab (an IL-6 inhibitor) decreased time to ICU discharge and mortality, preliminarily reported from the REMAP-CAP trial [21]. Lymphopenia that has been related to severe COVID-19 infection, ICU admission, acute respiratory distress syndrome, and mortality can be caused by some immunosuppressants, for examples, lymphocyte-depleting antibodies or antimetabolites [22], whereas m TOR have been related to interstitial pneumonitis development [23]. Most transplant centers will stop usage of these drugs. SpO_2/FiO_2 ratio < 440 or PaO_2/FiO_2 < 300 is related to a significant lower risk of intubation, ICU transfer, or death [24]. In severe-COVID-19-hypoxic LTRs, variable-doses glucocorticoids are frequently administered [25].

For the application of this issue, we now have some experience and insight for COVID-19-infected LTRs. We look forward to getting the optimal timing of COVID-19 vaccination adjustment of immunosuppression in LTRs, whereas the investigations of the T-cell response and additional COVID-19-vaccine doses are ongoing [26]. Nevertheless, the best methods to protect LTRs are facial masking, physical distancing, and COVID-19 vaccination.

Conclusion

Long-term outcomes of lung transplantation in severe COVID-19 patients are still to be investigated. National and international regulatory transplantation professional bodies should track the transplant-COVID-19 patient for establishing the standard guidelines.

Authors' Contributions

Dr. Attapon Cheepsattayakorn conducted the study framework and wrote the manuscript. Associate Professor Dr. Ruangrong Cheepsattayakorn and Professor Dr. Porntep Siriwanarangsun con-

tributed to scientific content and assistance in manuscript writing. All authors read and approved the final version of the manuscript.

Competing Interests

The authors declare that they have no actual or potential competing financial interests.

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