Lung Transplantation as a way to Escape Pneumonia in Patients with COVID-19: Lessons from ARDS and Influenza

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ABSTRAK

Pada masa kini, Coronavirus, yang disebut sebagai Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), virus yang mengancam jiwa dengan tingkat kematian yang tinggi (4,2%) dan belum ada pengobatan absolut, pada akhirnya dapat mengakibatkan sindrom gangguan pernafasan akut (ARDS). ARDS adalah salah satu komplikasi fatal, ditandai dengan infiltrasi paru dan hipoksemia berat. Kondisi ini dapat berkembang dari peradangan paru primer yang disebabkan oleh berbagai virus, terutama virus influenza, beberapa patogen manusia yang paling umum. Karena itu, banyak penelitian mengeksplorasi beberapa pendekatan untuk pengobatan ARDS. Transplantasi paru telah diklaim sebagai obat yang efisien untuk ARDS dan Influenza parah, yang juga dapat untuk mengobati komplikasi paru kritis pada SARS-CoV-2. Sepengetahuan kami, baru pertama kali studi untuk meninjau semua data yang tersedia tentang kemampuan transplantasi paru pada pengobatan pasien kritis dengan ARDS, influenza, dan SARS-CoV-2.

Kata kunci: *SARS-CoV-2, COVID-19, ARDS, influenza, lung transplantation.*

ABSTRACT

In this era, the novel Coronavirus, referred to as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a life-threatening virus with a high mortality rate (4.2%) and with no absolute treatment as of yet, may ultimately result in acute respiratory distress syndrome (ARDS). ARDS is one of the fatal complications, highlighted by pulmonary infiltration and severe hypoxemia. This condition can be developed from primary lung inflammation caused by various viruses, particularly influenza viruses, some of the most common human pathogens. Due to this

issue, many studies explored several approaches for ARDS treatment. Lung transplantation has been claimed as an efficient cure for severe ARDS and Influenza, which can also be offered for treating critical lung complications of SARS-CoV-2. Thereupon, to the best of our knowledge for the first time, we aimed to review all available data about capability of lung transplantation for the treatment of critically ill patients with ARDS, Influenza, and SARS-CoV-2.

Keywords: *SARS-CoV-2, COVID-19, ARDS, influenza, lung transplantation.*

INTRODUCTION

The latest danger against global health is the current outbreak of the respiratory disease that was given the name Coronavirus Disease 2019 (COVID-19). The first cases of Covid-19 were reported in December 2019. This coronavirus was structurally related to the virus responsible for Severe Acute Respiratory Syndrome (SARS).[1, 2] An experimental antiviral medication, remdesivir, received Emergency Use Authorization by the US Food and Drug Administration in 2020 for patients afflicted with severe COVID-19.[3] In addition, chloroquine and hydroxychloroquine were considered, as for decades they served as useful medications in prevention and treatment of chronic inflammatory diseases, including rheumatoid arthritis (RA).[4] Despite their use in the treatment of viral respiratory infections, no strongly established evidence was found for the effectiveness of chloroquine/hydroxychloroquine medication on SARS or Middle East Respiratory Syndrome (MERS).[5] In the lineup for new, more efficacious medical approaches, Lung transplantation (LT) is receiving more attention. LT is preferred for patients with end-stage lung related diseases or severe respiratory insufficiency. Also, bilateral lung recipients showed a higher survival rate.[6,7] LT, as the only therapy for end-stage ARDS, provided the final choice for these patients to avoid death. Therefore, patients with irreversible pulmonary fibrosis, like post-COVID-19 ARDS, can be analyzed carefully for the possibility of a LT. In the Lancet section for Respiratory Medicine, Lang et al.[8] provided a comprehensive report of a 44-year-old patient with COVID-19-associated ARDS, who underwent a pre-treatment transplant assessment process and was successfully treated with LT. In addition, for patients with persistent lung failure following COVID-19, in whom many weeks of supportive measures in the intensive care unit (ICU) has not shown any significant improvement, LT was offered as a choice of treatment. Although this treatment is lifesaving, the true impact of LT in the acute cases of COVID-19 may have little consideration.[9] According to the data and hypothesis that LT can be a beneficial treatment of ARDS and Influenza, its potential for curing end-stage COVID-19 patients should be assessed further. In this review, to the best of our knowledge for the first time we aimed to gather available data about the efficacy of LT in patients with respiratory diseases ARDS, Influenza, and COVID-19 to achieve a better perspective of this treatment in these patients.

CONSIDERATIONS IN A COVID-19 PATIENT EVALUATION FOR LT ELIGIBILITY

LT has been suggested as the savior treatment for selected COVID-19 patients present with persistent pulmonary disease despite several weeks or months of hospitalization in ICU.[10] There are ten considerations that should be taken into account during a COVID-19 patient evaluation for LT candidacy. First, patients must not be older than 65, as cases of older patients showed poorer outcomes. Second, candidates for surgery must have single-organ dysfunction only. Third, adequate time must be considered for recovery.[11] Fourth, there must be radiological documentation of refractory lung disease. Fifth, the patient must be informed and able to discuss about transplantation. They should understand the impact of surgery on their quality of life. Sixth, patients must receive adequate physical health care while on the waiting list, because of better outcomes in such cases.[12,13] Seventh, patients should be eligible for standard transplantation criteria such as sufficient body-mass index and absence of other notable comorbidities, including severe heart disease.[14] Eighth, the patient's recent SARS-

CoV-2 Polymerase Chain Reaction (PCR) result should be negative. Based on observations made so far, the post-surgery fatality rate is remarkably higher for patients tested positive for infectious diseases, even in asymptomatic cases.[15] Ninth, the surgical center should be qualified in performing high-risk surgeries, as this type of surgery on ARDS patients with Extracorporeal Membrane Oxygenation (ECMO) support is one of the highest-risk and most complicated procedures.[16] Tenth, a wide donor pool should be accessible to qualified surgical centers to maximize survival chance of patients on the waiting-list. This will retain fair and impartial organ donor allocation and provide life-saving organ transplantation for cases that have the greatest chance of survival.[17] Therefore, with ECMO support and fulfilling the aforementioned criteria, LT can be helpful in selected cases with severe, serious respiratory failure secondary to ARDS and COVID-19.

LT FOR COVID-19-ASSOCIATED ARDS IN PCR-POSITIVE PATIENTS

Although a large proportion of patients with COVID-19 develop asymptomatic or mild disease, about 10% transfer to ICU as a result of ARDS.[18,19] Mortality rates of up to 60% have been reported for these patients.[20,21] Lang et al.[8] reported the first case of LT for a confirmed SARS-CoV-2 patient, a 44-year-old female patient with symptoms of cough and fever and nothing remarkable in her past medical history, except mild psoriatic arthritis which was treated previously, and a diagnosis of idiopathic CD4 lymphocytopenia with no clinical significance. According to the comprehensive examination and interdisciplinary discussions, the patient's lungs had no potential for recovery and based on following considerations, transplantation was approved: (1) negative viral culture and high real-time polymerase chain reaction (RT-PCR) Ct values, (2) more than one month after the onset of SARS-CoV-2 infection, (3) no available alternative procedure, (4) a young patient with a single-organ failure, (5) a pre-septic condition originated from the patient's lungs, and (6) no other obvious barriers for long-term recovery. A sequential bilateral LT was carried out, the patient was transferred to the ICU in a stable condition, and was proned in order to improve the gas exchange and to decrease the pressure on the lower lobes of the lungs. Standard triple immunosuppression therapy was performed, and due to the fact that the patient was highly pre-sensitized, six additional treatment patterns of immune-absorption were done and antithymocyte globulin was provided. Regardless of the success of this procedure it is necessary to mention that most COVID-19 patients admitted to the ICU are older than the maximum age limit for transplantation or have other comorbidities that might not allow physicians to consider LT. This case report suggests that LT should be included in the therapeutic methods for COVID-19 positive patients with COVID-19-related ARDS. However, the applied criteria for patient selection and timing of LT still need to be validated in further studies.

PRE- AND POST-OPERATIVE MENTAL ASSESSMENT AND INTERVENTION FOR LT IN ELDERLY COVID-19 PATIENTS

Lyu et al.[22] reported the postoperative mental status of two elderly COVID-19 patients in China who had no history of psychiatric disorders prior to the COVID-19 infection. The first patient, a 66-year-old woman without any history of chronic disease, underwent a bilateral LT and her status was observed for 28 days thereafter. She had developed symptoms such as restlessness and confusion 27 days before surgery which lasted for 7 days. After achieving full consciousness 8 days after surgery, only psychological supportive treatments were administered to enhance her mood and sedatives such as zolpidem (10 mg/day) and olanzapine (5 mg/day) were prescribed to treat her insomnia. The mental status of the second patient, a 70-year-old man with a 5-year history of hypertension and a 10-year history of diabetes, was observed for 21 days. Consciousness was fully recovered 6 days after the LT surgery and similar to the first patient, sedatives were prescribed to treat episodes of insomnia. By the time the observation period was over, no sign of any mental disturbance was declared. Muscle rehabilitation training started in both patients 10 days after operation. In regard

of these data, providing intensive supportive care may avoid post operation acute brain dysfunction in COVID-19 patients.

COVID-19 AND IMMUNE RESPONSES BEFORE AND AFTER LT

A few COVID-19 patients were diagnosed with more severe conditions, including acute lung injury (ALI) and ARDS. As previously mentioned, LT may be a beneficial method to protect patients from COVID-19-related ARDS.[8,10] However, to attain safer outcomes, perioperative immune reactions of patients should be evaluated. The recent report by Yan et al.[20] surveyed the immune system reactions and the remnants of SARS-CoV-2 nucleic acids in two clinical cases before and after LT, including the very first case of LT for COVID-19 globally. They described two severely ill COVID-19 patients (group 1: a 58-year-old male with COVID-19-related ALI and ARDS) and (group 2: a 73-year-old male with COVID-19-associated multiple organ failure and ARDS). Both cases were admitted for LT, in order to be preserved from end-stage complications of COVID-19, in particular, ARDS. Whole blood lymphocytes, immunocytes (T, B, and NK cells), blood cytokines, and Ag-definite IgMs and IgGs of hospitalized COVID-19 patients were assessed. The number of lymphocytes in these cases remained below the standard amount before and after LT (<1.1×109/L). The levels of blood immunocyte subclass CD3+ CD45+ T were under 60% and a decrease of CD8+ T cells was observed ($P < 0.01$). Furthermore, together with viral replication, the IL-6 and IL-10 ranges in plasma overstepped the maximum limit of normal values. Total concentrations of cytokine IL-10, IL-4, IL-6, IFN-γ, and TNF-α in a severe period of disease were considerably higher compared to the convalescence period. These findings display weak humoral and cellular immune reactions in patients infected with COVID-19. In pathological analyses, the results of the second patient illustrated vague mature CD3+ cells in tissues and large-scale fibrosis and mucosal necrosis in the bronchioles, and the number of IgA+ cells in epithelial cells declined in both lung lobes. Residual COVID-19 in the lungs could be the main cause for the positive test result and mild symptoms in recovered SARS-CoV-2 patients, despite antiviral therapy. After the LT operation in severely ill COVID-19 patients (without antiviral treatments), there were no signs of COVID-19 infection in the transplanted lungs and no indication of residual COVID-19 nucleic acids observed on CT scans. Also, the humoral immune response was found to be negative. Moreover, according to Tabary et al.[23], COVID-19 is extremely devastating to the immune system, leading to the decrease of splenic T and B cell population as a result of necrosis and apoptosis. This may explain the incompetence of the immune system to protect the lungs from SARS-COV-2.

LT FOR ELDERLY PATIENTS WITH SEVERE COVID-19 PNEUMONIA

According to some studies, SARS-CoV-2 might result in irreversible loss of respiratory function in end-stage COVID-19 elderly patients.[24-26] The International Society for Heart and Lung Transplantation (ISHLT) mentioned that LT is considered to be an efficient treatment for end-stage chronic lung disease.[27-29] However, it is not recommended for patients with positive viral RNA tests since the ubiquitous virus may damage the transplanted lungs.[8,30] Thus, the viral RNA test should be negative at least twice before surgery and the specimen tested should be extracted via sputum and bronchoalveolar lavage (BAL). Han et al.[31] speculated that some factors such as blood transfusion or long-term medication, with high-doses of immunomodulators such as Thymallfasin, may be associated with early acute rejection. However, up to now, there hasn't been enough evidence to prove that irreversible lung injury may progress in SARS-CoV-2 lung infection patients.

Two patients with end-stage COVID-19 pneumonia who underwent LT were studied.[31] The first case was a 66-year-old woman diagnosed with COVID-19, who received medication as well as convalescent plasma therapy, but showed no improvement in her declining respiratory condition. Afterwards, the patient was tested for

SARS-CoV-2, and due to negative result (despite her "white lung" radiographs) she was enlisted for LT. There were no detectable signs of pleural effusion after surgery, but the oxygenation index started to decrease. There were some complications pointing towards acute rejection, but after one dose of steroid pulse therapy, the patient's oxygen saturation rapidly improved and the chest x-ray became clearer.

The other case was a 70-year-old man diagnosed with COVID-19, with progressive decline in his condition, despite receiving medication. His lungs in his most recent chest x-ray were described as a blurry X-ray Furthermore, after testing negative on the SARS-CoV-2 nucleic acid tests, LT was performed. Outcomes were virtually the same as the first patient: demonstrating clear chest x-rays with no evidence of pleural effusion and residual COVID-19 in the lungs.[31] Based on this study, LT could be an efficient intervention for end-stage COVID-19 patients when using medication, internal medicine guidelines, and mechanical ventilation (MV), where ECMO cannot ameliorate the lungs' deteriorating condition.

LT FOR PROGRESSIVE COVID-19 RELATED PULMONARY FIBROSIS

LT could be a potential life-saving procedure for patients with currently non-resolving COVID-19.[32,33] However, concerns limiting transplantation include recurrence of COVID-19 (or superinfecting pathogens associated with viral pneumonia), infection of the allograft, technical challenges imposed via virus-mediated injury to the patient's lung, and possible risk of allograft infection with ventilator-associated pathogens causing pneumonia. Severe COVID-19 related damage to pulmonary vessels and pleura could create practical barriers to transplantation, and severe deconditioning due to long-term MV together with sedation and blockade of neuromuscular function. There remains a lack of adequate evidence about the possibility of lung recovery after severe COVID-19 pneumonia, and whether it results in better long-term outcomes than LT.[32] In this regard, Bharat et al.[32] reported the first results of two successful LT surgeries in patients diagnosed with non-resolving SARSCoV-2 associated ARDS at the United States. Comparing the histology of explanted native lungs compared to the lungs of patients who expired from SARS-CoV-2 demonstrated some evidence of severe fibrosis in the former. The results of Single molecule Fluorescence In-Situ Hybridization (smFISH) for detecting COVID-19 RNA strands did not detect recurrent COVID-19 infection in the allograft. Therefore, LT may be the only choice for saving these patients.[32] Their study reported a case of a female in her 20s diagnosed with SARSCoV-2 showing the symptoms of severe and treatment-resistant hypoxemia despite different interventions (such as endotracheal tube placement and MV), with the level of oxygen in her blood progressively decreasing. Thus, she was listed for LT and later underwent the bilateral LT surgery. Post-operative care included the patient's current medication regime in addition to immunosuppressants. As well as her neurocognitive state, her muscular strength and endurance improved quickly following the transplantation. Two months after surgery, the patient was discharged home with oxygen saturation values of over 98% and was able to perform daily activities on her own.[32]

Another case of a man in his 60s diagnosed with SARSCoV-2, who also suffered from comorbid conditions, including recurrent Pseudomonas aeruginosa pneumonia and hemothorax, was reported. Despite attempting different treatment approaches, no improvement in lung compliance and oxygen saturation was seen, therefore he was listed for LT. Despite the similarity between his first two independent intraoperative assessments, unexpected complexity was reported because of colliquative necrosis following COVID-19 related Pseudomonas aeruginosa pneumonia. Thirty days after transplantation surgery, the patient respired on room air with oxygen saturations above 97%, and his status, including consciousness and muscular strength, improved over time, under the care of rehabilitation services.[32]

Moreover, according to the findings of this study, the lungs of both patients infected with SARS-CoV-2 were edematous and their

weight had significantly increased. Explanted lungs of both patients showed presence of pleural thickness and adherence, along with large bacterial cavities associated with necrosis. These bacteria were detected through PCR assay in BAL samples of the postoperative cultures. In addition, regions of diffuse alveolar hemorrhage, acute bronchopneumonia due to secondary bacterial infection, and uncommon micro thrombi were observed in the lungs of both cases. Lack of matrix organization was seen in the biopsies of patients who expired from severe SARSCoV-2 pneumonia as well as in the sections of lung explants from patients who underwent transplantation.[32]

LESSONS FROM LT TREATMENT FOR ARDS PATIENTS

According to American-European Consensus Conference (AECC), ARDS is the acute onset of decreasing oxygen levels in the blood, with bilateral intrusions on chest X-ray, without any evidence of left atrial hypertension.[34] Complications are seen as a result of sepsis, trauma, and pneumonia, although some patients may also have extra-pulmonary complications.[30] Coronaviruses that are highly pathogenic to humans such as SARS-COV, MERS-COV, and SARS-COV-2 have different symptoms, but one of the most important side effects is ALI or ARDS, which can even lead to death.[35] In patients with COVID-19, a phenomenon called cytokine storm is observed, which is also associated with lung damage, in which inflammatory cytokines are secreted in large quantities.[36] The exact mechanism of ARDS in COVID-19 patients is not known, but the abundant secretion of cytokines that induce inflammation such as IL-6, IL-1, and TNF-α may play an important role.[37-40]

Due to the critical condition of patients with ARDS, multiple studies were conducted on the effectiveness of various therapeutic interventions, including LT. Chang et al.[41], in a retrospective study, identified 305 patients with ARDS, including 14 patients with an average age of 39 (SD 11) years and 8 females with no underlying disease. However, there were only 3 patients with underlying diseases, all of whom were utilizing MV. Most of these patients were candidates for LT, the first major cause of ARDS in these patients being accidental inhalation of humidifier disinfectant and the second being pneumonia. The results of this study demonstrated that although LT may be able to lengthen the survival time of ARDS patients, it is in fact the final therapeutic option. More importantly, physicians should pay close attention to the reversibility of patients' lung function.

In another study conducted by Brichon et al.[42] a 32-year-old woman with acute myeloid leukemia was first treated with chemotherapy and autologous bone marrow transplantation, and three months later received ruminant interleukin 2 (lL-2). Since the patient developed ARDS 4 days after receiving ruminant lL-2, MV was required. Although many efforts were made to treat the patient, her condition worsened, and LT was performed as a final resort. After 11 months of follow-up, it was found that the patient was in good condition. Therefore, in this study, it was suggested that LT can be a suitable method in some patients with ARDS. According to the promising results obtained from these studies, the use of LT for the treatment of patients with ARDS can be concluded, and it was anticipated that LT may be useful in the treatment of patients with COVID-19 who have ARDS.

LESSONS FROM LT TREATMENT FOR INFLUENZA PATIENTS

Invasive pulmonary aspergillosis (IPA) is an uncommon disease presented in pediatric cases with impaired immune systems. However, it may also develop secondary to severe influenza A pneumonia in adults who were previously healthy. While fatality and morbidity rate reported among children is high, patients are commonly given antifungal medication for IPA prior to radiologic and clinical resolution. In addition, ECMO, also known as extracorporeal life support (ECLS), is gradually developing as a promising treatment especially in patients with intense respiratory failure. Bates et al.[43] reported a critical care unit admission for a 15-year-old case with respiratory distress induced by influenza A subtype H3. Due to his rapidly deteriorating condition, MV was required for

him. Furthermore, the growth of Aspergillus fumigatus led to increased serum galactomannan, and despite the administration of antifungal medications, bilateral intensive pulmonary necrosis developed. Afterwards, he received veno-venous ECMO (VV-ECMO) support. Since multiple organ failure markedly lowered his chance of recovery, he was eligible for lung transplant. Thereby, the patient underwent successful bilateral LT operation after his medical support changed to a right ventricular assist device (RVAD) and oxygenator. 40 days later, he was discharged in a stable condition.

Influenza A virus subtype H1N1 provokes a broad range of clinical syndromes, including self-limited illness andworst of all, ARDS.[44] In fact, Influenza A is capable of rapid progression to ARDS and pulmonary fibrosis. Pulmonary fibrosis secondary to Influenza A Pneumonia may cause lung dysfunction, however it rarely warrants LT.[45,46] Nonetheless, an established invaluable treatment for ARDS called ECMO is a bridging option for pulmonary transplantation, although its long-term usage is a highly controversial topic. Generally, influenza A is a communicable disease which presents with the same respiratory and gastrointestinal symptoms as COVID-19. To name a few: cough, fever, vomiting and diarrhea (particularly in pediatric patients). Manifestations vary from mild to severe, meaning some patients might show no symptoms while some might struggle with an irreversible stage of disease.[47]

Also, Dr. Lisa Maragakis pointed out more similarities in addition to what has just been cited. Both infectious viruses can be easily transmitted during their incubation period, however, this period is much longer in COVID-19. Moreover, pneumonia may develop secondary to these infections. Medications commonly administered are antiviral drugs, not antibiotics. If both diseases progress into more severe stages, hospitalization and assisted ventilation may be required.[48] In the following, few cases infected with different subtypes of influenza virus who eventually recovered due to LT will be reviewed. Qi Wang et al. reported a successfully performed bilateral LT in a 45-year-old man with H1N1-induced ARDS and progressive fibrosis who had received ECMO for the last 45 days before the operation.[49] His hospitalization and treatment processes are described below:

With no underlying lung disease, his only symptoms were cough and fever. As H1N1 pneumonia was diagnosed, he received oseltamivir. Evidence of bilateral pulmonary infiltration confirmed ARDS indicating the need for ventilation and ECMO. Also, tracheostomy along with continuous antibiotic therapy was used. Despite experiencing subsequent septic episodes, the H1N1 test result was negative, thus several antibiotics were administered. Even with immediate treatment measures for pulmonary fibrosis, the lungs were continuing to deteriorate. Therefore, he was included in the list of urgent recipients of LT and after about one week, a suitable 16-year-old donor free of infection was available. Ultimately, bilateral LT was operated successfully. On the first day after the operation, there was no longer a need for ECMO, on the 4th-day the ventilator was withdrawn, and on the 15th-day non-invasive ventilation via tracheostomy tube was stopped. Despite postoperative complications, including empyema, right ventricular (RV) failure, acute dysfunction of the liver and kidney, he recovered and was discharged 65 days later. After seven months, his condition was well and he could live independently, but he had signs of slightly reduced lung capacity plus elevated blood creatinine due to anti-rejection drugs.[2]

INFLUENZA 1

A severe respiratory illness associated with H1N1 virus, was identified in March 2009 in Mexico.[50] Rapid viral testing and PCR, with broad range of sensitivity, were used to detect this virus. Al Aklabi et al.[2] reported a case of a 50-year-old man who suffered from chronic obstructive pulmonary disease and end stage lung disease due to α1-antitrypsin deficiency. He was hospitalized and listed for bilateral LT, but 48 hours after the injection of latent H1N1 virus vaccine, he displayed non-specific symptoms such as malaise and myalgia. A nasopharyngeal swab was taken for PCR testing, then following the positive test result and ISHLT recommendations[51,52], oseltamivir was started.

After transplantation, two samples of BAL from the transplanted lung happened to be positive for H1N1 virus, resulting in antiviral and anti-rejection therapy prescription based on regular protocols which previously resulted in promising outcomes. Finally, he was discharged home in a good condition 21 days after the operation. Thus, it can be concluded that LT can be successful in pandemic periods if careful clinical evaluation sand laboratory screenings are performed on both donors and recipients.

INFLUENZA 2

Patients with suppressed immune system are at high risk for developing severe influenza A (H1N1) disease. D. P. Mason et al.[53] reported a case of 65-year-old man who suffered from end-stage interstitial lung disease and was admitted for unilateral transplantation. Before his operation, the recipient complained of a mild sore throat with no fever, malaise, and rhinorrhea, and had a normal chest x-ray. RT-PCR for influenza was positive 17 days after original nasopharyngeal swab; however postoperative BAL cultures were negative for both allograft and native lungs. 4 hours after transplantation he became agitated due to a body temperature of 40.0°C thus Oseltamivir (Tamiflu) was started empirically. During 48 hours, he developed worsening hypoxemia and increasing consolidation of the allograft. He received Peramivir after consideration of the high risk of renal insufficiency, disseminated intravascular coagulation and interrupted limb ischemia. Seventy-two hours after starting peramivir, he began to recover dramatically and chest x-rays gradually cleared. Despite these positive outcomes, the overall prognosis was assessed as poor and he died 22 days after the operation. This case report shows the important lasting threat of influenza H1N1 for patients who receive thoracic organ transplants, especially unilateral LT because of the airborne nature of the pathogen. Therefore, recommendations of ISHLT should be taken seriously: avoidance of contact with symptomatic individuals, vaccination of all H1N1 influenza patients listed for transplantation, and recipients who show even subtle signs and symptoms of upper respiratory infection or unusual infectious symptoms should be swabbed for H1N1, scheduling surgery only when results are available.[51]

Fever, shortness of breath, cough, expectoration, as well as laboratory tests, such as Lymphopenia and an increased level of C-reactive protein are similar both influenza and COVID-19.[54] So it can be hypothesized that due to success in LT in influenza, the use of LT in COVID-19 cases may be useful too, but caution should be exercised when selecting patients, ensuring that they meet 10-item criteria (previously mentioned), including a negative RT-PCR test before the operating in both the donor and recipient, due to high risk of severe infection.

CONCLUSION

Despite, a large number of efforts to find treatments for critically ill patients with COVID-19 in the medical world, there is no effective treatment for end-stage SARS-CoV-2 infected patients. Moreover, conventional antiviral therapies may not be beneficial and some patients experience the end-stage acute respiratory syndrome. LT provided the potential effectiveness for the treatment of these patients and rescued them from death. Since SARS-CoV-2 has similarities to the flu and ARDS, and a number of articles have recently begun to examine the positive effect of LT on the treatment of COVID-19. Therefore, this review aimed to collect all the data on this subject, gaining experiences from ARDS and the flu for LT. Satisfactory results after LT in improving the general condition have arisen the researcher's efforts to find a better method for the treatment of acute respiratory syndrome COVID-19. This review shows that LT could be used when medical treatments consisting of ventilation and ECOM could not modify the lung action., and could be a promising choice.

CONFLICTS OF INTEREST

There is no conflict of interest on this article.

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