

Review Article

Reports Of Two Cases Concerning Lung Transplant Recipients And Covid-19.

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Abstract

Despite the WHO's declaration that the pandemic emergency is over, patients with impaired immune systems are still at risk from COVID-19. Over the past two years, the COVID-19 pandemic has spread over the world and claimed a considerable number of lives. Although the initial lethality of SARS-CoV-2 has diminished after three years, immunocompromised patients have a much worse prognosis despite an initially positive clinical course following COVID-19. The patient's condition rapidly worsened and they passed away within a few days as a result of substantial lung involvement. This instance demonstrates how unpredictable COVID-19 patients are in comparison to the general population, particularly those who have had lung transplants. Two interesting case reports that illustrate the intricate difficulties associated with COVID-19 infection in lung transplant recipients are presented in this publication. The initial instance focuses on a patient who underwent a kidney transplant in 2022 after receiving a bilateral lung transplant in 2009 for pulmonary artery hypertension. Despite a promising clinical outcome at first after catching COVID-19, the patient's condition quickly worsened and, as a result of widespread lung involvement, they passed away within a few days. This example demonstrates the unpredictability of COVID-19 and its potentially fatal effects on recipients of lung transplants. The second instance is a patient who suffered from chronic obstructive pulmonary disease (COPD) and had bilateral lung transplantation five years prior. In addition to having pre-existing conditions such as diffuse bronchial stenosis and chronic lung allograft rejection (CLAD), this person also got COVID-19. The patient's clinical state rapidly worsened after the viral infection, with bronchial stenosis getting worse. This instance demonstrates how COVID-19 can make pre-existing lung issues worse in transplant recipients. These incidents demonstrate the critical necessity for heightened awareness and specialized treatment approaches when it comes to COVID-19 in lung transplant recipients. The disease's unpredictable and harmful progression in these individuals emphasizes how crucial it is to put tight preventative measures in place for this susceptible group, including immunization and rigorous adherence to infection control procedures. To fully comprehend the distinct dynamics of COVID-19 in lung transplant recipients and to create focused therapies to enhance their results, more research is necessary.

Keywords : lung transplant; COVID-19; chronic lung allograft rejection.

INTRODUCTION

Even though the World Health Organization (WHO) announced on May 5, 2023, that the pandemic emergency was over, COVID-19 is still very much alive and well, particularly when it comes to susceptible groups like recipients of solid organ transplants. The Centers for Disease Control and Prevention state that fever, coughing, shortness of breath, muscle aches, and, in certain situations, loss of taste or smell are the typical symptoms of COVID-19. Additionally, there may be digestive symptoms such as nausea, vomiting, diarrhea, and abnormal liver function. Headache, lightheadedness, conjunctivitis, eye irritation, and a rash with red skin are less frequent symptoms [1]. The prognosis, clinical characteristics, and management of COVID-19 in susceptible patient groups, such as those who have received lung transplantation (LT) and allogeneic

stem cell transplantation (allo SCT), have been the subject of numerous retrospective investigations in recent years [2,3]. These studies offer important new information about how to treat and manage these particular patient groups. Analyzing the effects of COVID-19 in recipients of allo SCT was the goal of a study carried out in transplant hospitals in Germany and Austria. 130 patients who had previously received allo SCT and then contracted SARS-CoV-2 between February 2020 and July 2021 were included in the cohort. The median age at allo SCT was 55 years old, while the median age at COVID-19 diagnosis was 59 years old. Acute myeloid leukemia and Hodgkin's and non-Hodgkin's illnesses were prevalent underlying conditions among the patients. myelodysplastic syndrome, acute lymphoblastic leukemia, and lymphoma. At the time of their COVID-19 diagnosis, several patients had active graft versus host disease (GVHD) that need systemic immunosuppressive

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treatment, and many were in incomplete remission. The most widely used COVID-19 detection technique was nasopharyngeal swab Polymerase Chain Reaction (PCR). The primary setting for transmission was the house and family. The majority of patients developed pneumonia, and symptoms like fever, cough, dyspnea, and exhaustion were prevalent. About 19% of patients needed intensive care, and some of them got special medications such as bamlanivimab, remdesivir, convalescent plasma, and corticosteroids. In order to underscore the need for a thorough understanding of the effects of COVID-19, this study sought to identify risk factors for severe disease and mortality in allo SCT recipients with the virus. On this patient group in order to direct suitable management tactics and enhance patient care. The clinical features and prognosis of LT patients with COVID-19 were also examined in a retrospective, multicenter cohort research carried out in French lung transplant institutions [4]. Thirty-five LT recipients with confirmed or highly suspected SARS-CoV-2 infection were included in the study. With a median time to LT of 38.2 months, double lung transplants were the most prevalent procedure. For these patients, immunosuppressive treatments such as corticosteroids and calcineurin inhibitors were frequently employed. Fever was the most common symptom, though clinical presentation varied. CT scans of the chest usually revealed ground-glass opacities. Infections acquired in hospitals, healthcare facilities, and the community were reported in the study. Among the management techniques were the modification of immunosuppressive medication and the use of particular antiviral medications like remdesivir and hydroxychloroquine. The study found that, following a median follow-up of 50 days, the overall survival rate was 85.7%. However, acute respiratory distress syndrome (ARDS) and multi-organ failure claimed the lives of five patients. Some patients experienced lung superinfections and thrombotic episodes. In LT recipients with COVID-19, overweight status was found to be a possible risk factor for death; however, no other significant risk variables for severe illness or mortality were discovered. Furthermore, investigations and research are being carried out to evaluate the safety and efficacy of the COVID-19 vaccine in recipients of lung transplants, offering important information and direction for their medical care. Antirecipients, offering insightful advice on how to manage their healthcare. One of the most important weapons in the fight against the worldwide epidemic has been the COVID-19 vaccine. The creation and dissemination of potent vaccines gives promise for a more secure and healthful future. Vaccines lessen the severity of symptoms, avoid hospitalizations, and save lives by boosting the immune system's ability to identify and combat the virus. But the significance of vaccination is significantly greater for those who have received lung transplants. Because of their often compromised immune systems,

transplant recipients are more susceptible to infections. Vaccinating against COVID-19 can reduce the risk of serious illness or problems in this susceptible group and offer an extra layer of protection. For precise immunization recommendations and protocols, transplant recipients must speak with their healthcare specialists. The clinical features and prognosis of COVID-19 in allo SCT and LT patients are better understood thanks to these investigations, which also emphasize the significance of specialized care approaches for this susceptible group. To fully comprehend the risk factors and best practices for managing COVID-19 in various patient groups, more study is required.

CASE #1

A 58-year-old man with a history of ischemic heart disease, normal cardiac function, osteoporosis, and obesity was the first patient to contract COVID-19. In 2009, he received bilateral lung transplantation using intraoperative veno-arterial extra corporeal membrane oxygenation (ECMO) for idiopathic pulmonary hypertension. He was kept on mechanical ventilation for 17 days and did not require extended ECMO support in the intensive care unit. Other than lobar pneumonia, which was managed with targeted antibiotic therapy, and atrial fibrillation, which necessitated pharmaceutical cardioversion, he did not experience any significant early postoperative problems. On day 47 after surgery, he was sent home. He experienced severe renal insufficiency that necessitated peritoneal dialysis after developing chronic renal failure as a result of long-term use of calcineurin inhibitors. On October 15, 2022, he had a kidney transplant after being considered for one. After fulfilling the frailty criteria, he was given three doses of an mRNA anti-COVID-19 vaccine at the beginning of the pandemic immunization campaign, but he did not produce a SARS-CoV-2 antibody response. Two months before receiving a kidney transplant, he also had treatment with tixagevimab/cilgavimab following a positive COVID-19 serology test. The illness in this instance remained asymptomatic. His mean creatinine was 2 mg/dL (normal <1.2 mg/dL), indicating inadequate renal function following the kidney transplant. After the kidney transplant, his lung function was still below ideal, but the most recent endoscopic biopsy revealed an early chronic allograft rejection-like pattern. The patient first appeared on December 8, 2022, with mild upper respiratory symptoms and showed positive results from an antigen swab test for COVID-19. Antimetabolites, calcineurin inhibitors, and corticosteroids were all part of the patient's immunosuppressive treatment at the time. His clinical history remained stable with a modest symptomatic condition, and molnupiravir was promptly provided without altering immunosuppressive medication. The patient arrived at the emergency room with coughing

and dyspnea twenty days following the first positive test. A CT scan of the chest revealed a constant volume of right pleural effusion along with modest bilateral infiltrates. The patient was admitted to the hospital for observation because of the chest CT results and the ongoing positive antigen swab test. Five days later, he was released in a stable clinical state, with steady renal function and no signs of respiratory failure. As directed, the immunosuppressants were taken consistently. But after that, the patient's condition worsened, as evidenced by follow-up chest CT scans showing increasing lung infiltrates and progressive respiratory failure. He was consequently readmitted to our hospital's lung transplant center on January 7, 2023, where he was diagnosed with acute respiratory distress syndrome and placed in an intensive care unit box. Between December 2022 and January 2023, his lung parenchymal involvement grew worse, as seen in Figure 1. To treat the severe COVID-19 infection, the medical team chose to stop using calcineurin inhibitors and antimetabolites. Despite starting a broad-spectrum antibiotic called piperacillin/tazobactam, the patient's gas-exchange performance steadily declined and the chest CT results showed no improvement. More pulmonary infiltrates were visible on later chest X-rays. Remdesivir, an antiviral medication, was contemplated as a final treatment option. Nevertheless, the patient's condition worsened in spite of these attempts, and on January 19, 2023, he passed away.

CASE #2

In our center, we have seen a second unusual instance of COVID-19 in lung transplant recipients. In 2017, a 52-year-old man with alpha 1 antitrypsin deficiency had bilateral lung transplants for panlobular and centrilobular emphysema. He received ECMO support through aorto-atrial cannulation during the transplant. He was extubated on the second post-operative day after the transplant and did not require ECMO extension. He had satisfactory respiratory function and was released from the intensive care unit after five days. He stayed for sixteen days. He had subcutaneous emphysema when he visited the outpatient clinic six days after being sent home. Immediately after, an urgent CT scan revealed moderate pneumomediastinum, pneumothorax, and pneumopericardium. A little dehiscence of the left bronchial anastomosis was discovered during bronchoscopy. A little dehiscence of the left bronchial anastomosis was discovered during bronchoscopy. He was sent right away to the Interventional Pulmonology Unit, where he received endoscopic fibrin glue treatment before being sent home. But three months later, the patient's left major bronchus experienced severe bronchial stenosis. A residual lumen of 5 mm remained after multiple unsuccessful attempts at treating this disease with laser and mechanical dilatation. Significant

stenosis later developed in the patient's right upper and middle lobe bronchi as well as left upper lobe. He was still being monitored at our lung transplant facility. The March 2021 CT scan revealed subtotal blockage of the left upper lobar bronchus with atelectasis of the left upper lobe, stenosis of the right lobar bronchus, and malacic degeneration of the bottom third of the trachea. The CT scan, which was done in March 2021, revealed bronchial stenosis but no signs of pneumonia (Figure 2). During follow-up, a bronchial biopsy revealed early chronic lung allograft failure, and *Pseudomonas aeruginosa* cultures were positive. In order to eliminate the bacterial colonization, he was treated with antibiotics and immunosuppressive medication that included corticosteroids, calcineurin inhibitors, and antimetabolites. Three doses of mRNA anti-COVID-19 had been administered to the patient. vaccination and had a reaction to antibodies. With a forced expiratory volume in one second (FEV1) of 35% and a forced vital capacity (FVC) of 45%, his respiratory function was slightly compromised, but this was constant over time. The 6-minute walk test revealed no signs of desaturation. The patient was treated with nirmatrelvir and ritonavir after testing positive for COVID-19 on July 5, 2022, and presenting with a persistent cough and dyspnea. Once more, the immunosuppressive regimen consisting of antimetabolites, calcineurin inhibitors, and corticosteroids remained unchanged. Following a negative COVID-19 test, the patient arrived at our facility in July 2022 for a standard outpatient assessment with significantly worsening respiratory function, exhibiting a FEV1 of 30% and a FEV1/FVC ratio of 45 percent. The radiological pattern of the chest CT scan, which included a left pneumothorax and oedema of the left main bronchus, was similar to that of bronchitis and was thought to be a COVID-19-related development of the partial atelectasis that had already been detected on the prior CT scan. For a follow-up bronchoscopy and potential lobectomy, an urgent hospital stay was scheduled. The patient's condition significantly worsened, and endoscopy showed that the bilateral bronchial stenosis was progressing negatively. Considering the ineffectiveness of both endoscopic He was evaluated for retransplantation due to the quick and severe deterioration in lung function after the infection, as well as the (bronchial balloon dilation) and surgical (lobectomy of atelectatic lobe) treatments. Following the normalization of his inflammatory indicators and the attainment of 92% oxygen saturation following daily respiratory physiotherapy, he was released. But in February 2023, the patient's respiratory condition worsened much more, and he was readmitted to the hospital. A few days later, he passed away from untreatable type-2 respiratory failure brought on by left-sided pneumonia. Figure 2 shows how the development of pneumonia and pleural effusion exacerbated the lung parenchymal involvement.

DISCUSSION

The entire scientific community faced a global threat in the form of COVID-19. However, more effective treatments have been developed over time as a result of growing understanding of the virus's physiopathology. At the moment, we must be mindful of the possible danger that COVID-19 presents to patients who are already fragile. Due to their ongoing immunosuppression, solid-organ patients are particularly vulnerable to severe COVID-19 infections. Due to increased immunosuppression, a high rate of allograft rejection, and graft exposure to the environment, this risk is much greater for recipients of lung transplants [5,6]. Although pulmonary hypertension accounted for the bulk of lung transplants performed at our center over the previous four years, the cases discussed in this research also relate to parenchymal diseases such as emphysema in addition to vascular lung pathology. This is to draw attention to the disparate starting circumstances that brought the two patients to these peculiar situations. We believe that the most intriguing discovery is the entirely different course of the disease in terms of the timing of its progression and its radiological and clinical manifestations. The second crucial element is the various approaches taken: in the first instance, medical care was altered, whereas in the second instance, we first chose to list for retransplantation after considering endoscopic bronchial dilatation or surgical resection, which was ultimately decided against due to the procedure's futility. The final piece of evidence from our cases relates to the identification of potential risk factors, which include bronchial stenosis, immunosuppressive medication, and CLAD. Fever and cough are the primary clinical manifestations of COVID-19 in transplant recipients, as observed in non-immunocompromised hosts, particularly following the introduction of anti-COVID-19 vaccinations [4]. This pattern is supported by our patient cohort: of the 60 lung transplant recipients our team monitored, 30 contracted COVID-19, but only two of them experienced a serious infection. It is crucial to remember that this patient series has not yet been published. The occurrence of ground-glass opacities on CT, which are common in the general population, is a characteristic of the radiological results [4]. The primary radiological finding of COVID-19 in lung transplant recipients is also ground-glass opacities; however, radiological presentation can differ from person to person and be impacted by variables like scan timing, disease severity, and the existence of pre-existing lung conditions or transplant-related anatomical changes. Each of the two documented examples had distinct characteristics. Interestingly, one month after testing positive for the virus, Case #1 specifically developed a clinically significant type of COVID-19. The patient's respiratory condition significantly worsened 30 days after infection, even after receiving

molnupiravir medication. The patient's immune system was likely severely compromised by the recent kidney transplant, which increased his vulnerability to COVID-19. Lung transplant recipients and solid-organ recipients in general exhibit a longer viral clearance of SARS-CoV-2 than the general population—nearly 3–5 weeks—according to Raja et al. It is believed that the first player in the antiviral response is T-cell immunity, which is pharmacologically suppressed upon transplantation [7]. However, after reviewing 77 publications, Opsomer et al. found no correlation between the kind of immunosuppression and death [8]. Additionally, they discovered a less significant immune response following the initial two immunization doses. Altneu et al. support the necessity of a fourth dose in recipients, particularly those infected with the Omicron variety, and corroborate these findings [9]. In Case #2, COVID-19 aided in hastening the respiratory decline of a patient who already had severe bilateral bronchial stenosis. Since the immunocompromised patient's late start of COVID-19-related pneumonia has never been reported in lung transplant recipients, we believe Case #1 to have a fairly odd element. As a result, we think that these two case reports show different ways that COVID-19 manifests in lung transplant recipients. Due to parenchymal involvement, we observed a late-onset ARDS in the first instance. The pathophysiological mechanism in the second instance is more closely linked to the involvement of big bronchial structures. This draws attention to a few crucial elements. The severe weakness of these individuals, both during the acute phase and a month following infection, is the topic that is more frequently covered in the literature. The treatment plan for COVID-19 infection consists of stopping antimetabolites and increasing corticosteroids, either with or without stopping calcineurin inhibitors. Remdesivir or lopinavir–ritonavir are two examples of the particular antiviral medications used to treat the illness [4]. For Case #1, medical therapy was the only method of treatment. Although there are no clear rules on when to stop using antimetabolites, we could speculate that the beginning of severe pneumonia could be caused by a late therapy change. A major factor in the development of the parenchymal involvement in Case #1 was most likely the alteration of immunosuppressive medication. According to the French Transplant Society, the course of treatment ought to be determined by how severe the illness is [4]. The most frequent modification to immunosuppressive treatment in this latter trial was likewise the removal of antimetabolites, which was followed by an increase in the dosage of corticosteroids [4]. However, as every transplant institution has a different approach based on the patient's clinical parameters, no clear indication can be made. However, in Case #2, we saw that the bronchial stenosis was getting worse. In this instance, the medication approach proved ineffective, so we turned to surgery as a last resort

with no chance of success. The literature did not provide any comparable cases for comparison. These instances demonstrate possible predictors of lung transplant patients' development of COVID-19-related illness. The research reports that between 10% and 46% of lung transplant recipients die from COVID-19. Thirty of the sixty patients in our sample of lung transplant recipients contracted COVID-19, resulting in a 6.6% mortality rate (2/30 patients). There has never been a publication on this patient group. To explain these facts, we suggest two explanations. First, during the early stages of the pandemic, when there were no vaccines, we saw a high degree of adherence to the COVID-19 requirements (isolation, mask wear, etc.) in Italy, which reduced the rate of infection even among our transplant community as a whole. Second, the bulk of COVID-19 infections in our group were detected in the second wave, when vaccination rates were already high and infection symptoms were consequently lower. In terms of long-term follow-up following COVID-19 infection, it has been demonstrated that while the TLC and DLCO dramatically dropped as a result of the infection's restrictive pattern and interstitial involvement, the FEV1 remained stable [4]. Kamp and associates demonstrated that a poor result in this patient group was predicted by the burden of comorbidities as measured by the Charlson Comorbidity Index [5]. Furthermore, overweight status (body mass index >25 and <30 kg/m²) was linked to a higher risk of death, according to Messika et al. [4]. It should be highlighted that none of these individuals got any vaccinations before contracting CLAD, and that COVID-19 may be a significant factor in deciding the clinical course in terms of death (43% of cases) or a further drop in the FEV1 (43% of cases). While Kamp et al. stated that their series had a lower risk of CLAD, Messika et al. revealed a lower mortality rate of 14.3%. Permpalung et al. found no evidence of a significant correlation between COVID-19 and the potential exacerbation of pre-existing CLAD [10], whereas a shorter observation time and a lower median age and BMI [4,5]. These incidents highlight the need for us to be mindful of the potential long-term inefficiency of both acute therapies like antiviral therapy, social isolation, and vaccinations. In fact, the fragility of lung transplant recipients may render all prophylactic measures useless. Lastly, it's important to never undervalue the connection between viral damage and post-transplant anatomical alterations like bronchial stenosis. As in Case #1, there is minimal indication of bronchial alterations following SARS-CoV-2 infection. But according to Kanne et al., bronchial thickening is a frequent side effect of prolonged COVID-19 [11]. In their analysis of a Brazilian cohort of pulmonary COVID-19, Visconti et al. discovered numerous late infection problems. Two months after discharge, they found that the rate of bronchial thickening, as determined by CT scans, was 18% [12].

To sum up, the first example emphasizes the difficulties confronted by COVID-19 transplant patients, especially those with complicated medical histories and immunosuppressive treatments. Although the entire range of viral effects on lung structure is still unknown, it is logical to believe that the COVID-19 infection was the main cause of the bronchial tree's eventual closure in Case Report #2. The patient's experience emphasizes the necessity of ongoing observation, customized treatment plans, and additional study to enhance COVID-19 care and results in this susceptible group. Based on the second case report, we also think that SARS-CoV-2 may affect the bronchus in vulnerable patients and worsen stenosis or bronchiectasis.

CONCLUSIONS

Conclusion Lung transplant recipients have faced many difficulties as a result of the COVID-19 pandemic, but better care and results will come from continued research and a deeper comprehension of the virus. Patients who have received lung transplants are extremely fragile, and if they test positive for COVID-19, they need to be evaluated and treated right away if they have CLAD. When lung transplant recipients contract COVID-19, the existence of transplant complications—whether morphological (like bronchial stenosis) or immunological (like CLAD)—must be regarded as a risk factor for a poor prognosis. The development of severe disease is significantly influenced by immunosuppressive medication, and a late pharmacological adjustment may be harmful to the patient's health. Data on the population of transplant recipients is scarce, and COVID-19 is a relatively new occurrence. Population, and COVID-19 is a new occurrence with a lot of unidentified features. Protecting this susceptible group requires ongoing adherence to preventive measures like immunization and social separation. To fully understand the effects of SARS-CoV-2 infection in lung transplant recipients, more research is required.

Author Contributions

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Institutional Review Board Statement

Because this study was observational and descriptive in

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Informed Consent Statement

Every participant in the study gave their informed consent.

Conflicts of Interest

No conflicts of interest are disclosed by the writers.

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