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# COVID-Related Chronic Allograft Dysfunction in Lung Transplant Recipients: Long-Term Follow-up Results from Infections Occurring in the Pre-vaccination Era

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**Abstract:** Introduction: We report on characteristics and lung function outcomes among lung transplant recipients (LTRs) after COVID-19 with infections occurring in the first year of the coronavirus pandemic prior to introduction of the vaccines. Methods: This was a retrospective study of 18 LTRs who tested positive for SARS-CoV-2 between 1 February 2020 and 1 March 2021. The mean age was 49.9 (22–68) years; 12 patients (67%) were male. Two patients died due to severe COVID-19. Results: During the study period, there were 18 lung transplant recipients with a community-acquired SARS-CoV-2 infection. In this cohort, seven had mild, nine had moderate, and two had severe COVID-19. All patients with mild and moderate COVID-19 survived, but the two patients with severe COVID-19 died in the intensive care unit while intubated and on mechanical ventilation. Most patients with moderate COVID-19 showed a permanent lung function decrease that did not improve after 12 months. Conclusion: A majority of LTRs in the current cohort did not experience an alteration in the trajectory of FEV1 evolution after developing SARS-CoV-2 infection. However, in the patients with moderate COVID-19, most patients had a decline in the FEV1 that was present after 1 month after recovery and did not improve or even deteriorated further after 12 months. In LTRs, COVID-19 can have long-lasting effects on pulmonary function. Treatment strategies that influence this trajectory are needed.

**Keywords:** chronic lung allograft dysfunction; community-acquired respiratory viral infection; CLAD hypothesis



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## 1. Introduction

Community-acquired respiratory virus (CARV) infections pose a significant challenge among lung transplant recipients (LTRs). The rate of infection among LTRs is much higher than in other solid organ recipients due to the direct exposure of the lung to the potentially hostile external environment. Other risk factors contributing to the infection risk are severe immunosuppression, the blunted cough reflex due to lung denervation, poor lymphatic drainage, and impaired mucociliary clearance as a result of ischemic injury to the bronchial mucosa and narrowing of the bronchial anastomosis [1]. Compared to bacterial respiratory infections, viral infections initially lead to less severe symptoms, but then lead to a greater worsening of the lung function [2]. In LTRs, CARV can lead to both acute and chronic allograft dysfunction [3–8].

The mechanisms behind allograft dysfunction are only partly understood, hampering the establishment of adequate treatment. It has been suggested that symptomatic respiratory viral infections after lung transplantation elicit immune responses to lung self-antigens by inducing circulating exosomes that contain lung-associated self-antigens [9]. CARV infections may activate alloimmune responses, leading to post-CARV chronic lung allograft dysfunction (CLAD) [7].

Since the first successful human lung transplantation in 1983 [10], the overall 5-year survival rates in lung transplantation are still only approximately 50–70%, which is considerably worse compared to other solid organ transplantations, even after significant improvements in donor selection, organ preservation, perioperative management, and better treatment of post-operative complications [11].

CLAD is the leading cause of death beyond the first year after lung transplantation. Currently, there is no medical treatment that can cure CLAD. Several treatments have been introduced in an attempt to slow the progression of CLAD such as azithromycin, pravastatin, montelukast, extracorporeal photopheresis, and total lymphoid irradiation [12–16].

Symptomatic respiratory viral infections were shown to be independently associated with CLAD [7]. In LTRs, CLAD is a progressive and in most patients irreversible process, and a major cause of long-term allograft failure and death. CLAD has two different main phenotypes called bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). About 70% of LTRs with CLAD have the BOS phenotype.

In CLAD-BOS, there is a persistent decline in the forced expiratory volume in 1 s (FEV1) associated with an obstructive ventilatory defect; whereas in CLAD-RAS, there is a restrictive defect with an increased FEV1/forced vital capacity (FVC) ratio or a decrease in FVC or total lung capacity (TLC). It was observed in a prior study that CLAD-RAS could develop after COVID-19 [17]. Mahan et al. showed a significant loss of lung function in 18 LTRs (40.9%), of which 3 patients (5.6%) developed CLAD-RAS. Prior studies have shown a strong association between respiratory viral infections and the development of CLAD in which symptomatic viral infections demonstrated a stronger relationship with CLAD [17–20].

Data on long-term effects of CARV due to infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in LTRs are scarce. Infection by SARS-CoV-2 can be highly variable in disease severity, ranging from mild upper respiratory distress to fulminant viral pneumonitis with multi-organ failure and death. In this study, we evaluated the impact of SARS-CoV-2 infection in LTRs during the first year after the infection.

## 2. Methods

This was a single-center, retrospective-chart-review study. The study population consisted of consecutive adult LTRs $\geq$ 18 years of age with COVID-19 at the University Hospital Zurich, Switzerland, in which formal informed consent was given. The infection with SARS-CoV-2 was demonstrated using real-time reverse transcriptase polymerase chain reaction (RT-PCR).

Patients with COVID-19 were classified as "mild" when clinical symptoms consisted of mild constitutional symptoms, fever, or a dry cough. Patients were classified as "moderate" COVID-19 when the clinical symptoms including dyspnea with or without hypoxia and where chest imaging was abnormal (infiltrates and/or ground-glass opacities). The baseline characteristics of these patients were published previously [21]. Full recovery was defined as two negative SARS-CoV-2 RT-PCR tests at least 24 h apart along with the resolution of symptoms. Patients with acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), or cardiac failure were classified as "severe" COVID-19.

All spirometric testing was conducted in the lung transplant clinic using a Geratherm respiratory spirometer (Geratherm Medical AG). The spirometry analysis was performed according to the Standardization of Spirometry by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [22]. CLAD-BOS and CLAD-RAS were defined according to the classification by Verleden [12]. CLAD-BOS stage 0 was defined as FEV1 > 90% of baseline, BOS stage 1 as FEV1 decline of 66–80% of baseline, BOS stage 2 as FEV1 decline of 51–65%, and BOS stage 3 as an FEV1 decline $\leq$ 50% of baseline. CLAD-RAS was defined as a total lung capacity (TLC) decline > 10% or an FEV1/FVC > 0.70.

Using the pre-infection baseline FEV1 ($FEV1_{pre}$) and post-infection FEV1 ($FEV1_{post}$), we calculated the change in lung function as follows: $(FEV1_{pre} - FEV1_{post})/FEV1_{pre}$.

### 3. Statistical Analysis

Descriptive statistics were performed; the main data are summarized in Tables 1–4. The results are reported as the mean with the range and categorical variables were calculated as counts (*n*) and percentages (%).

**Table 1.** Non-vaccinated lung transplant recipients with mild and moderate COVID.

| Pat | Age, m/f | FEV1 Pre | FVC Pre | FEV1 1m | FEV1 3m | FEV1 6m | FEV1 12m | %FEV1 Δ 1m | %FEV1 Δ 12m | %FVC Δ 12m |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 56, f | 2800 (104%) | 2810 (96%) | 2880 (113%) | 2770 (111%) | 2820 (113%) | NA | +2.9% | NA | +1.1% |
| 2 | 22, f | 1710 (57%) | 2250 (86%) | 1810 (61%) | 1880 (63%) | 2050 (69%) | 2030 (68%) | +16% | +16% | +16.4% |
| 3 | 27, m | 2750 (71%) | 3610 (79%) | 2640 (69%) | 2730 (71%) | 2500 (65%) | 2490 (66%) | −4.0% | −9.45% | −1.98% |
| 4 | 64, m | 2010 (56%) | 2470 (58%) | 2050 (66%) | 2030 (66%) | 2010 (60%) | 1910 (57%) | +1.99% | −4.98% | +18.2% |
| 5 | 34, m | 1520 (33%) | 3030 (54%) | NA | 1340 (30%) | 1190 (27%) | 1120 (25%) | NA | −26.3% | −8.99% |
| 6 | 19, f | 2400 (62%) | 2340 (73%) | NA | NA | 2840 (79%) | 2730 (77%) | NA | +13.8% | +17% |
| 7 | 67, f | 1660 (89%) | 2380 (105%) | NA | 1530 (83%) | 1650 (89%) | 1500 (68%) | NA | −9.64% | −4.39% |

Abbreviations: m = male; f = female; FEV1 pre = forced expiratory volume in 1 s pre-COVID; FEV1 1m, 3m, 6m, 12m = forced expiratory volume in 1 s after 1, 3, 6, and 12 months, respectively; %FEV1 Δ 1m, 12m = $(FEV1_{pre} - FEV1_{post})/FEV1_{pre}$ 1 month or 12 months after recovery from COVID, respectively; FVC = forced vital capacity; %FVC1 Δ 12m = $(FVC_{pre} - FVC_{post})/FVC_{pre}$ 12 months after recovery from COVID; NA = not applicable.

**Table 2.** Non-vaccinated lung transplant recipients with moderate COVID.

| Pat | Age, m/f | FEV1 Pre | FVC Pre | FEV1 1m | FEV1 3m | FEV1 6m | FEV1 12m | %FEV1 Δ 1m | %FEV1 Δ 12m | %FVC Δ 12m |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 28, m | 3430 (69%) | 4970 (81%) | 3330 (61%) | 3160 (58%) | 3610 (66%) | 3680 (68%) | −2.92% | +7.29% | +1% |
| 2 | 48, m | 3000 (89%) | 3730 (90%) | NA | 2570 (72%) | 2730 (77%) | 2840 (80%) | NA | −5.33% | −10% |
| 3 | 38, m | 1610 (46%) | 3210 (74%) | NA | 1100 (31%) | 1320 (39%) | 1360 (39%) | NA | −15.5% | −2.2% |
| 4 | 68, m | 2430 (79%) | 3090 (76%) | 2370 (80%) | 1980 (64%) | 2660 (86%) | 2140 (74%) | −2.47% | −11.9% | −12.4% |
| 5 | 66, m | 2180 (78%) | 2930 (81%) | 1980 (71%) | 2330 (82%) | 1560 (55%) | 1300 (47%) | −9.17% | −40.4% | −20.6% |
| 6 | 49, f | 1430 (52%) | 1700 (53%) | 1500 (55%) | 1480 (54%) | NA | 1440 (50%) | +4.90% | +0.70% | +13.7% |
| 7 | 68, m | 3160 (97%) | 4420 (103%) | 3010 (92%) | 3320 (105%) | NA | NA | −4.75% | NA | NA |
| 8 | 64, f | 2450 (89%) | 3340 (94%) | 2020 (76%) | NA | 2340 (85%) | 1910 (70%) | −17.6% | −22.0% | −37.4% |
| 9 | 63, m | 4530 (127%) | 4990 (107%) | NA | 3440 (96%) | 4250 (120%) | 3940 (111%) | NA | −13.0% | −10.8% |

Abbreviations: Pat = patient number; m = male; f = female; FEV1 pre = forced expiratory volume in 1 s pre-COVID; FEV1 1m, 3m, 6m, 12m = forced expiratory volume in 1 s after 1, 3, 6, and 12 months, respectively; %FEV1 Δ 1m, 12m = $(FEV1_{pre} - FEV1_{post})/FEV1_{pre}$ 1 month or 12 months after recovery from COVID, respectively; FVC = forced vital capacity; %FVC1 Δ 12m = $(FVC_{pre} - FVC_{post})/FVC_{pre}$ 12 months after recovery from COVID; NA = not applicable.

**Table 3.** Pre-COVID chronic lung allograft dysfunction (CLAD) and donor-specific antibody (DSA) monitoring (mild COVID).

| Pat | CLAD Pre-COVID | DSA Pre-COVID | DSA Post-COVID < 3 mo. | DSA Post-COVID 3–6 mo. | DSA Post-COVID 6–12 mo. |
|---|---|---|---|---|---|
| 1 | BOS 0 | Neg | DQ2 MFI-2124 | Neg. | Neg. |
| 2 | BOS 0 | Neg. | DQ6 MFI-4224 | DQ6 MFI-1827 | Cw5 MFI-826<br>DR52 MFI-1207<br>DQ6 MFI-1278 |
| 3 | BOS 0p | DQ8 MFI-3949 | N/A | N/A | DQ8 MFI-1417 |
| 4 | BOS 0 | DQ2 MFI-2260 | No data | DQ2 MFI-572 | No data |
| 5 | BOS 3 | DQ2 MFI-6628<br>DP1 MFI-1280 | Neg. | N/A | DQ2 MFI-7222<br>DP1 MFI-2264 |
| 6 | BOS 0 | Neg. | Neg. | Neg. | Neg. |
| 7 | BOS 0p | Neg. | N/A | Neg. | Neg. |

**Table 4.** Pre-COVID chronic lung allograft dysfunction (CLAD) and donor-specific antibody (DSA) monitoring (moderate COVID).

| Pat | CLAD Pre-COVID | DSA Pre-COVID | DSA Post-COVID < 3 mo. | DSA Post-COVID 3–6 mo. | DSA Post-COVID 6–12 mo. |
|---|---|---|---|---|---|
| 1 | BOS 1 | Neg. | Neg. | N/A | Neg. |
| 2 | BOS 0 | Neg. | Neg. | N/A | Neg. |
| 3 | BOS 3 | Neg. | N/A | Neg. | Neg. |
| 4 | BOS 1 | Neg. | Neg. | N/A | Neg. |
| 5 | BOS 3 | DR18 MFI-1802<br>DR51 MFI-610<br>DQ2 MFI 24,766 | DR18 MFI-1308<br>DQ2 MFI 20,201 | DR18 MFI-1538<br>DR51 MFI-875<br>DR52 MFI-888<br>DQ2 MFI 18,100 | DR18 MFI-1250<br>DQ2 MFI 15,223 |
| 6 | BOS 0p | Neg. | N/A | N/A | Neg. |
| 7 | BOS 1 | Neg. | Neg. | N/A | Neg. |
| 8 | BOS 1 | Neg. | Neg. | N/A | Neg. |
| 9 | BOS 0 | Neg. | Neg. | Neg. | Neg. |

## 4. Ethical Considerations

The study was granted approval by the Zurich branch of the Swiss Medical Ethics Committee (Swissethics No. 2021-00293).

## 5. Results

During the study period, there were 18 episodes of SARS-CoV-2 infection among the LTRs, all of which were community-acquired. The lung function data are shown in Table 1 (mild COVID-19) and Table 2 (moderate COVID-19). The mean age was 49.9 (22–68) years; 12 of the LTRs (67%) were male.

In the group of patients with mild COVID-19, the mean C-reactive protein level (CRP) was 29.8 (4–77) mg/L; while in moderate COVID-19, the mean CRP was 58.2 (4.8–140) mg/L. In mild COVID-19, the mean creatinine level (119 µmol/L, range 60–166) was less than in moderate COVID-19 (mean creatinine 231 µmol/L, range 17–809). In both the mild and moderate COVID-19 patients, there was no obesity (mean body mass index 22.4 and 26.3 kg/m$^2$, respectively) observed. All patients were under chronic triple immunosuppressive therapy, including prednisone in all (100%) of the patients. In the mild COVID-19 patients, this included cyclosporine A in one (14%), tacrolimus in six (86%) rapamycin in one

(14%), and mycophenolate mofetil in six (86%) of the patients. In the moderate COVID-19 patients, the immunosuppression included cyclosporine A in three (33%), tacrolimus in four (44%), and everolimus in one (11%) of the patients. During the active infection with SARS-CoV-2, in all patients mycophenolate mofetil was then discontinued as part of our standard practice.

Although we discontinued mycophenolate mofetil, most patients did not develop donor-specific antibodies (DSA), as shown in Tables 3 and 4.

The pre-transplant diagnosis was cystic fibrosis (CF) in four (57%), chronic obstructive pulmonary disease (COPD) in one (14%), and interstitial lung disease (ILD) in two (29%) patients in the group of patients with mild COVID-19, while in the group of moderate COVID-19 patients, this was CF in two (22%), COPD in four (44%), ILD in two (22%), and pulmonary arterial hypertension in one (11%) of the patients.

Two LTRs died due to severe COVID-19; these patients were intubated and therefore there were no post-COVID lung function data available. Since the only two patients with severe COVID-19 did not survive the infection, they are not shown in a separate table. The median age was 58.5 years (range 56–61); both were male with a mean BMI of 31.2 kg/m$^2$. Both patients had very high CRP levels (mean 302 mg/L, range 199–406) and chronic kidney failure (mean creatinine 208, µmol/L, range 202–213). Both had interstitial lung disease as the pre-transplant diagnosis. Empiric antibiotic treatment was standard in all patients, both ambulatory and hospitalized. As the evolution of COVID-19 was favorable in most patients, additional microbiology samples were not indicated. Only in severe cases were additional samples performed; these patients were intubated and finally died.

## 6. Discussion

This retrospective study in LTRs with COVID-19 showed lung function decline after COVID-19 in most patients with moderate COVID-19. In most patients with mild COVID-19 evolution, the lung function evolution was not affected. Patients who showed lung function decline after COVID-19 in the first month did not recover in the following year, and in this group of patients, most showed a further lung function deterioration. After 12 months, 10 patients (56%) showed a decreased FEV1 as compared to pre-COVID FEV1 measurements, with a FEV1 range of −4.98% to −40.4%. In four patients ($n$ = 22%), the FEV1 decrease was 5–10%, three patients ($n$ = 17%) lost ≥ 10–20%, and three patients ($n$ = 17%) lost ≥ 20%. Most patients did not develop DSA even one year post-COVID.

Although CLAD-BOS was frequently diagnosed after moderate COVID-19, we had no patients with CLAD-RAS or a mixed phenotype. These results were in line with a retrospective multicenter study that collected data from three Dutch transplant centers and included 74 LTRs that showed a significantly lower lung function that remained significantly lower compared to the pre-COVID-19 values [23].

The so-called wild type of the SARS-CoV-2 was first demonstrated in China at the end of 2019. Relevant virus mutations were the Alpha variant (B.1.1.7, first demonstrated in the United Kingdom in September 2020), followed by the Beta variant (mutation E484K, first seen in South Africa in May 2020), the Gamma variant (P.1, initially detected in Brazil, in November 2020), the Delta variant (B.1.617.2, initially detected in India in May 2021), and the Omicron variant (November 2021).

Although a genotyping PCR was not initially performed at our hospital, the above-described patients were studied between 1 February 2020 and 1 March 2021 and probably mainly suffered from the wild type, Alpha variant, Beta variant, or the Gamma variant of SARS-CoV-2 based on the predominant strains detected in this period.

The numbers of affected patients at that time (beginning of the pandemic) were relatively small. The second wave of the pandemic in Switzerland was in October 2020 [24]. At the beginning of the pandemic's spread in Switzerland, specifically in March 2020, there were only 3000 COVID-19 patients diagnosed despite widespread testing, but this rapidly increased to over 500,000 in January 2021 [25].

At the time of this study, patients had not yet received the vaccinations because they were not yet available. The approval of the first COVID-19 mRNA vaccine, called BNT162b2 (Pfizer BioNTech) [26], was on 19 December 2020, followed by the COVID mRNA vaccine by Moderna, which was approved on 12 January 2021 in Switzerland [27]. Moreover, at this time there were no clear guidelines on how to deal with immunosuppression in LTRs with COVID-19 and vaccination uptake was slightly delayed due to prioritization of elderly persons at the beginning of the vaccine roll-out.

We now know that vaccination in lung transplant recipients is a key strategy that reduces the risk of severe COVID-19 and hospitalization [28]. Vaccination is also now considered as an indirect treatment in the prevention of CLAD BOS in LTRs due to SARS-CoV-2 infection. Unfortunately, two problems in vaccination of LTRs have become evident. The first problem is that LTRs have a blunted humoral and cellular immune response after COVID-19 vaccination [29]. The second is a shorter duration of the protective effects of the vaccine [29–32].

A weaker immune response was demonstrated in immunosuppressed transplant recipients who received the trivalent influenza vaccine; these patients showed significantly lower antibody titers [33]. Another study also showed a weaker response in immunosuppressed heart transplant recipients after pneumococcal vaccination [34]. In LTRs, the standard therapy is a triple immunosuppression in which most patients receive a combination of a calcineurin inhibitor (CNI), a mycophenolate derivative such as mycophenolate mofetil (MMF), and a corticosteroid (typically prednisone or prednisolone) [35]. All types of immunosuppressive drugs have different mechanisms of action that when combined will severely blunt the immune response. CNI blocks T-cell activation and proliferation, MMF impairs the proliferation of B and T lymphocytes and increases apoptosis, while corticosteroids mainly affect T lymphocytes by impairing their development, survival, activation, and migration [36].

Our study had some obvious limitations, namely the small number of patients, the single-center experience, and the retrospective design of the study. The data should therefore be interpreted with caution; for firm conclusions, further studies are needed.

In other viral infections in LTRs, acute rejection and chronic lung allograft dysfunction are well-known complications as well [37]. Allograft dysfunction is not only caused by direct effects of viral replication, but also by immunologically mediated lung injury [37]. The exact mechanisms are only partially understood.

In conclusion, this study suggested a potential relationship between SARS-CoV-2 infection and CLAD. More specifically, our hypothesis was that the risk of the development of CLAD-BOS was higher in the LTRs with moderate COVID-19 compared to those with mild COVID-19. Moreover, the decline in FEV1 could already be seen as soon as 1 month after COVID, with an additional FEV1 deterioration in the following months.

In LTRs, emphasis on prevention of COVID-19 by minimizing exposure and widespread use of vaccinations is certainly warranted because the increased severity of SARS-CoV-2 infections appears to increase the risk of CLAD development. The exact role of vaccination in LTRs requires further studies that include long-term follow-up data on FEV1 evolutions for different clinical situations because the current serological data show a suboptimal antibody response in these immunosuppressed patients. Thus, the protective effects regarding COVID-19 severity and disease course are not well studied to date.

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