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TRANSPLANT INFECTIOUS DISEASE

BRIEF COMMUNICATION

Impact of COVID-19 on long-term lung function in lung transplant recipients: A single-center retrospective cohort study

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Abstract

Available data are limited concerning long-term lung function (LF) evolution after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in lung transplant (LT) recipients. The aim of this study is to determine the effect of first SARS-CoV-2 infection on long-term LF in LT recipients. We analyzed spirometry results of LT recipients followed at our institution (March 2020 to July 2022) at 3, 6, and 12 months after first SARS-CoV-2 infection. Overall, 42 LT patients of our cohort (70%) with COVID-19 were included for long-term LF analysis. Forced expiratory volume in 1 s (FEV_1) declined significantly at 3 months (−4.5%, −97 mL, 95% CI [−163; −31], $p < .01$), but not at 6 and 12 months (−3.9%, −65 mL, 95% CI [−168; +39], $p = .21$). Results were quite similar for the forced vital capacity. Spirometry values declined significantly at 3 months after COVID-19 in LT recipients, presented a mixed decline at 6 months, and no significant decline at 12 months.

KEYWORDS
COVID-19, lung function, lung transplant recipients, lung transplantation, spirometry

Abbreviations: CLAD, chronic lung allograft dysfunction; COVID-19, coronavirus disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LF, lung function; LT, lung transplant; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1 | INTRODUCTION

Lung transplant (LT) recipients represent one of the highest risk groups for mortality from coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] Previous studies showed that non-SARS-CoV-2 coronavirus infections did not impact lung function (LF) evolution in this patient population.[3] Only two recent studies have investigated LF changes following COVID-19 infection in LT recipients.[4,5] The follow-up however was limited to 3–6 months, and intercurrent respiratory infections were not reported. The aim of this study is to determine the effect of first SARS-CoV-2 infection on long-term LF in LT recipients.

2 | MATERIALS AND METHODS

This observational, retrospective, single-center study was conducted at the Lausanne University Hospital, Switzerland. Our institution, one of the two lung transplantation centers in Switzerland, performs 20–25 lung transplantations yearly. The study was approved by the local ethics committee (Swiss-ethics 2022-00324).

All adult (≥18 years old) LT recipients diagnosed with a microbiologically proven SARS-CoV-2 infection by real-time PCR between March 1, 2020 and July 31, 2022 were included. Exclusion criteria were refusal of the institution's general consent for research, SARS-CoV-2 infection within 6 months from transplantation, and absence of follow-up spirometry (6 months or later) after the first SARS-CoV-2 infection.

The evolution of LF (FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity) was analyzed in patients with proven first COVID-19. The most recent spirometry performed within the last 6 months prior the first positive-SARS-CoV-2 PCR was considered as the baseline, and was compared to the measures at 3, 6, and 12 months after the first positive-SARS-CoV-2 PCR. FEV_1 and FVC values prior to the administration of beta-2 agonists were analyzed. Each maneuver was assessed according to the American Thoracic Society (ATS)–European Respiratory Society (ERS) standards.[6] Reference values were applied according to GLI-2012.[7]

Chronic lung allograft dysfunction (CLAD) was defined as persistent decline of 20% or more in FEV_1 value from the best baseline value post transplantation according to International Society for Heart and Lung Transplantation (ISHLT) criteria.[8] Spirometry trends were also analyzed for LT recipients with CLAD at baseline and for those who developed a bacterial or viral respiratory infection, including SARS-CoV-2 reinfection, within 12 months after first COVID-19.

A control group without SARS-CoV-2 infection until January 1, 2022 and with two spirometry measurements 12 months apart within the last 3 years was included.

LF variable with continuous variables was analyzed with paired *t*-test and signed-rank Wilcoxon test. Subject-specific FEV_1 and FVC variations in subgroups were analyzed with Mann–Whitney test or *t*-test. All statistical tests were two-tailed, and $p < .05$ was considered significant. We used the Stata version 17.0 software (StataCorp) for statistical analyses.

3 | RESULTS

From the 60 patients with SARS-CoV-2 infection in our cohort,[9] 10 (17%) were excluded due to a less than 6-month follow-up, seven (11%) due to a first SARS-CoV-2 infection within 6 months from transplantation, and one (2%) deceased during follow-up (40 days post-infection). Baseline patients' characteristics are shown in Table 1.

Significant FEV_1 decline from baseline was observed at 3 months (ΔFEV_1 −4.5%, −97 mL, 95% CI [−163; −31], $p < .01$, $n = 35$), but not at 6 months (ΔFEV_1, −2.2%, −57 mL [−118; +4], $p = .07$, $n = 42$) and 12 months (ΔFEV_1 −3.9%, −65 mL, 95% CI [−168; +39], $p = .21$, $n = 24$). Results were quite similar for FVC (Figure 1), with a significant decline at 3 months (ΔFVC −4.1%, −119 mL, 95% CI [−200; −39], $p < .01$) and 6 months (ΔFVC −3.2%, −103 mL, 95% CI [−183; −22], $p = .01$), but a lack of difference at 12 months (ΔFVC −3.1%, −99 mL, 95% CI [−238; +40], $p = .15$). Median FEV_1 and FVC declines are summarized in Table S1.

The decline of FEV_1 and FVC was quite similar in LT recipients subgroups with pre-existing CLAD, infection during omicron variant period, and even in cases within intercurrent bacterial or viral infection during follow-up. The median loss of FVC in the CLAD group was slightly more pronounced (−110 vs. −10 mL), but nonsignificant ($p = .09$). Among the different treatment groups, FVC declined significantly at 3 months only in subjects receiving dexamethasone (−275 mL vs. −60 mL, $p = .03$). This difference in decline then decreased and was found no longer significant at 6 and 12 months. The other declined FEV_1 and FVC were similar. (Table S1, in the appendices).

One patient (2%) developed CLAD (phenotype bronchiolitis obliterans syndrome) during follow-up. Sars-CoV-2 was diagnosed in October 2020, that is prior the vaccine was available and before the delta and omicron variants.

A group of 30 patients without SARS-CoV-2 infections was included as control. The first spirometry was performed from March 2019 to October 2020, while the second was obtained 12 months after. The FEV_1 and FVC declines were, respectively, −77 mL/year (SD ± 380) and −57 mL/year (SD ± 318) for the mean, −25 and 0 mL/year for the median (Figure S2 in the appendices). The FEV_1 and FVC declines at 12 months were not statistically different from the SARS-CoV-2-positive patients.

4 | DISCUSSION

In this study, we followed LT recipients up until 1 year after the first SARS-CoV-2 infection, and we did not observe a significant long-term decline in terms of FEV_1 and FVC. In the first year of the pandemic, there was a great fear in the lung transplantation community that SARS-CoV-2 could trigger chronic lung allograft in many recipients. We can now reassure LT recipients regarding the medium-term evolution of lung volumes in cases of COVID infection. Functional trajectories after lung transplantation are highly variable. Lung physiologic aging in adults is characterized by a progressive decline in FEV_1 between 18 and 47 mL/year (median 22 mL/year),[10] and in long-term

Characteristics	mean mL [CI95%] / %from baseline	p-value
FEV1		
3 months (n=35)	-97 [-163; -31] / -4.5%	<0.01
6 months	-57 [-118; +4] / -2.2%	0.07
12 months (n=24)	-65 [-168; +39] / -3.5%	0.21
FVC		
3 months (n=35)	-119 [-200; -39] / -4.1%	<0.01
6 months	-103 [-183; -22] / -3.2%	0.01
12 months (n=24)	-99 [-238; +40] / -3.1%	0.15

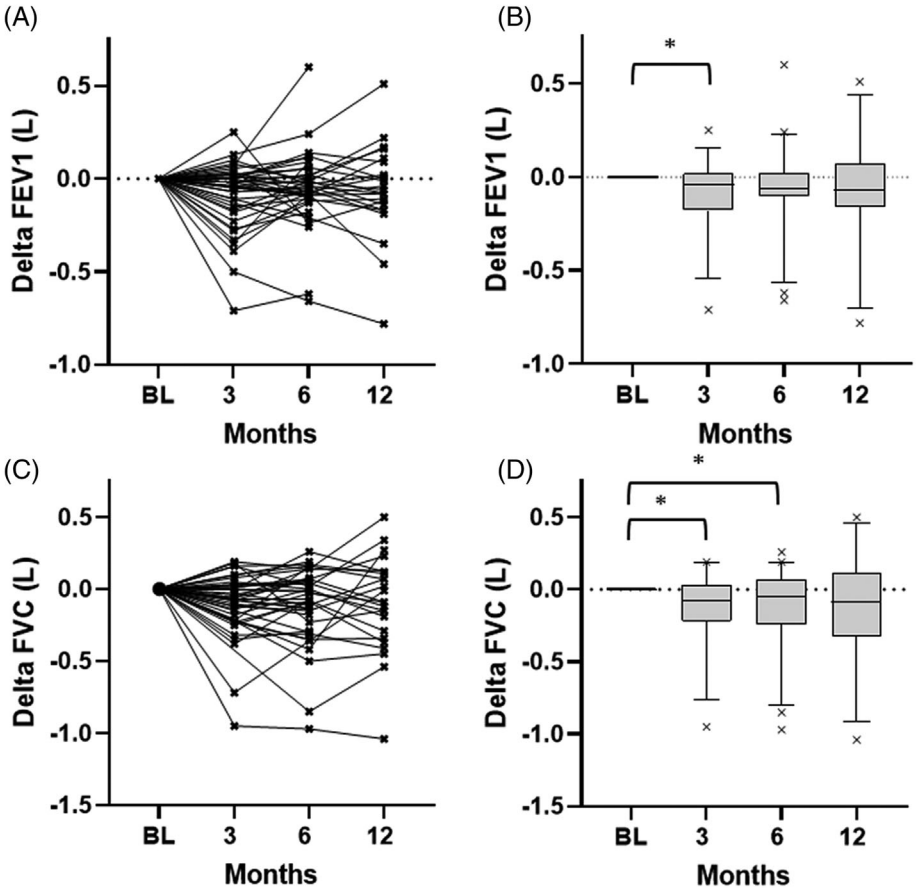

FIGURE 1 Decline of FEV_1 and FVC from baseline. FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity.

surviving (>15 years) LT recipients, the median annual FEV_1 decline is about 34 mL.[11] In our group of 30 non-infected lung recipients, the mean and median FEV_1 declines were, respectively, measured at −77 and −25 mL over 1 year.

Previous studies have shown a trend toward an LF decline at 3 months[4,5] after SARS-CoV-2 infection, and a gradual improvement at 6 months without reaching pre-COVID-19 values.[5] A multicenter retrospective study of 74 LT recipients recently showed such a similar trend; however, this study included more severe cases as indicated by a higher hospitalization rate (57% vs. 31%) and in-hospital mortality rate (20% vs. 7%) compared to our cohort.[4] A more significant decline in FVC than FEV_1 was also described suggesting a restrictive pattern.[4] In our cohort, we observed a significant decline of both FEV_1 and FVC at 3 months, without a predominant trend on FVC. We also noted a recovery of the FEV_1 at 6 months, with stability at 12 months. The decline in FVC did not seem to persist at 12 months, but a larger sample size might be needed to confirm these long-term results. Trindade et al. found a significant decline of FEV_1 at 3 months limited to the Delta-variant era; however, after the inclusion of all variants ($n = 103$), the rate of FEV_1 and FVC was similar before and at 3 months after infection.[5]

These results are similar to those described in LT recipients presenting non-COVID-19 respiratory viral infections as picornavirus,[3] human metapneumovirus,[12] respiratory syncytial virus,[3,12] or parainfluenza virus.[12]

Patients with CLAD had a quite similar LF evolution after COVID-19 in this study, as observed by Roosma et al.[4] Even after successive respiratory bacterial or viral infections, LF did not decrease significantly over time in patients with pre-existing CLAD. We found only a slight nonsignificant difference in FVC decline at 6 months in the CLAD

TABLE 1 Characteristics of lung transplant patients with SARS-CoV-2 infection.

Characteristics	All patients ($n = 42$)
Demographics	
Female sex, *n* (%)	20 (48%)
Age in years, mean [min–max]	55.6 [26–76]
Comorbidities	
Hypertension, *n* (%)	21 (50%)
Chronic kidney disease, *n* (%)	28 (67%)
Diabetes mellitus, *n* (%)	21 (50%)
Malignancy	5 (12%)
BMI ≥30 kg/m^2, *n* (%)	6 (14%)
Oxygen treatment at home, *n* (%)	5 (12%)
Charlson Comorbidity Index, median [Q1–Q3]	4 [3–5]
Transplantation data	
Primary diagnosis	
Chronic obstructive pulmonary disease, *n* (%)	17 (40%)
Cystic fibrosis, *n* (%)	11 (26%)
Other, *n* (%)	14 (33%)
Years from transplantation, mean [min–max]	8.5 [1–30.3]
Combined lung and other organ transplantation, *n* (%)	1 (2%)
Immunosuppressive treatment	
Tacrolimus, *n* (%)	41 (98%)
Cyclosporine, *n* (%)	1 (2%)
Mycophenolic acid, *n* (%)	40 (95%)
Azathioprine, *n* (%)	1 (2%)
Prednisone, *n* (%)	42 (100%)
Other, *n* (%)	1 (2%)
CLAD, *n* (%)	12 (29%)
BOS, *n* (%)	12 (29%)
RAS, *n* (%)	1 (2%)
Baseline spirometry	
FEV_1 in mL, mean [95% CI]	2401 [2148–2654]
FVC in mL, mean [95% CI]	3269 [2978–3559]
COVID-19 infection	
Infection since January 2022 omicron variant era, *n* (%)	28 (67%)
Vaccinated at least one dose before infection, *n* (%)	33 (79%)
2 doses	5 (12%)
3 doses	28 (67%)
Vaccinated a least one dose before infection or during follow-up	36 (86%)
Any COVID-19 treatment[a]	32 (76%)
Dexamethasone	8 (19%)
Sotrovimab	22 (52%)
Hospitalization for COVID-19-related symptoms, *n* (%)	13 (31%)
Oxygen therapy, *n* (%)	12 (29%)
Nonmechanical ventilation or Optiflow, *n* (%)	3 (7%)
Mechanical ventilation, *n* (%)	3 (7%)
Intercurrent bacterial or viral infection within 12 months after first COVID-19 infection	17 (41%)
Viral, *n* (%)	12 (29%)
Bacterial,[b] *n* (%)	5 (12%)
Death during follow-up[c]	1 (2%)

Note: Malignancy referred to solid organ or hematologic. Q1 = first quartile, Q3 = third quartile.

Abbreviations: BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; COVID-19, coronavirus disease 2019; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LF, lung function; LTR, lung transplant recipients; RAS, restrictive allograft syndrome.

[a]Included remdesivir, sotrovimab, dexamethasone, convalescent plasma, casirivimab, and imdevimab.

[b]One subject with *Haemophilius influenza* 9.3 weeks after COVID-19 infection, one subject with *Escherischia coli* 32.9 weeks after COVID-19 infection, one subject with *Mycobacterium xenopi* 16.6 weeks after COVID-19 infection, and two subjects with unknown bacteria 17.0 and 46.5 weeks after COVID-19 infection.

[c]Death from complications of COVID-19 infection.

group, which was not observed at 3 and 12 months. This finding is in contrast with the study of Kamp et al., showing a substantial functional deterioration in patients with pre-existing CLAD at 3 months post infection.[13] The incidence of CLAD during the 2.2-year period in our cohort was lower ($n = 1$; 2%) to that previously reported by Mahan et al. ($n = 3$, 6% during 1.0-year period[14]) and Roosma et al. ($n = 6$; 8% during 1.5-year period[4]). Patients treated with dexamethasone presented a higher decline only in FVC at 3 months, which was no longer significant at 6 and 12 months, probably because the most severe infections were treated with dexamethasone. There was no difference among LT recipients treated with sotrovimab. Finally, the group of patients with additional viral or bacterial infections occurring after COVID-19 onset ($n = 17$) did show comparable functional follow-up compared to the others.

Strengths of our study include a monocentric approach, the consideration of intercurrent respiratory infections, and the large availability of long-term (6–12 months) LF values in our cohort. Limitations of our study include the retrospective design, a relatively small sample size, and the changing epidemiology of COVID-19 and management (anti-SARS-CoV-2 treatment, vaccination) of LT recipients during the 2-year study period.[9] Due to the pandemic, which led us to cancel a large number of follow-up visits from March 2020, we often had only one spirometry test in the months preceding the infection to define the baseline spirometry values.

In conclusion, spirometry values declined significantly at 3 months after COVID-19 in LT recipients, presented a mixed decline at

6 months, and no significant decline at 12 months, even in cases with pre-existing CLAD. Recovery in LT recipients seems possible in the long-term despite an initial loss of dynamic volume.

AUTHOR CONTRIBUTIONS

Conceptualization: Alessio Casutt and Nahal Mansouri. Methodology: Alessio Casutt, Matthaios Papadimitriou-Olivgeris, Angela Koutsokera, John-David Aubert, and Brice Touilloux. Software: Matthaios Papadimitriou-Olivgeris and Brice Touilloux. Formal analysis: Alessio Casutt, Cédric Bongard, Foteini Ioakeim, and Brice Touilloux. Investigation: Alessio Casutt, Foteini Ioakeim, and Cédric Bongard. Data curation: Alessio Casutt, Foteini Ioakeim, Matthaios Papadimitriou-Olivgeris, Brice Touilloux, and John-David Aubert. Writing: Alessio Casutt, Matthaios Papadimitriou-Olivgeris, and Brice Touilloux. Original draft preparation: Alessio Casutt. Writing-review: Foteini Ioakeim, Matthaios Papadimitriou-Olivgeris, Cédric Bongard, Nahal Mansouri, and John-David Aubert. Editing: Nahal Mansouri, Angela Koutsokera, John-David Aubert, Brice Touilloux, and John-David Aubert. Supervision: Oriol Manuel, John-David Aubert, and Angela Koutsokera. Project administration: John-David Aubert and Angela Koutsokera.

CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

ETHICS STATEMENT

The local ethics committee (no. 2022-00324) approved this project.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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