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The effect of COVID-19 on transplant function and development of CLAD in lung transplant patients: A multicenter experience

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BACKGROUND: Concerns have been raised on the impact of coronavirus disease (COVID-19) on lung transplant (LTx) patients. The aim of this study was to evaluate the transplant function pre- and post-COVID-19 in LTx patients.

METHODS: Data were retrospectively collected from LTx patients with confirmed COVID-19 from all 3 Dutch transplant centers, between February 2020 and September 2021. Spirometry results were collected pre-COVID-19, 3- and 6-months post infection.

RESULTS: Seventy-four LTx patients were included. Forty-two (57%) patients were admitted, 19 (26%) to the intensive care unit (ICU). The in-hospital mortality was 20%. Twelve out of 19 ICU patients died (63%), a further 3 died on general wards. Patients with available spirometry (78% at 3 months, 65% at 6 months) showed a significant decline in mean forced expiratory volume in 1 second (FEV1) (ΔFEV1 138 ± 39 ml, p = 0.001), and forced vital capacity (FVC) (ΔFVC 233 ± 74 ml, p = 0.000) 3 months post infection. Lung function improved slightly from 3 to 6 months after COVID-19 (ΔFEV1 24 ± 38 ml; ΔFVC 100 ± 46 ml), but remained significantly lower than pre-COVID-19 values (ΔFEV1 86 ml ± 36 ml, p = 0.021; ΔFVC 117 ± 35 ml, p = 0.012). FEV1/FVC was > 0.70.

CONCLUSIONS: In LTx patients COVID-19 results in high mortality in hospitalized patients. Lung function declined 3 months after infection and gradually improved at 6 months, but remained...
Severe acute respiratory syndrome coronavirus—2 (SARS—CoV—2), which is responsible for coronavirus disease 2019 (COVID—19), has emerged as a global health threat. As of December 19, 2021, over 273 million COVID—19 cases and over 5.3 million deaths have been reported globally.\(^1\) Mortality rates from COVID—19 vary across countries, reflecting differences in population measures taken and social behavior, as well as in case identification, death registration, access to medical care and variable thresholds for hospitalization. The overall in-hospital mortality is around 15% to 20%, but up to 40% among patients admitted to the intensive care unit (ICU).\(^2\)

Concerns have been raised on the impact of COVID—19 on solid organ transplant (SOT) recipients, since SOT-recipients are at higher risk for severe COVID—19 as a result of chronic immunosuppression.

Several case series have been published on COVID—19 after solid organ transplantation and showed a higher mortality rate in SOT-recipients compared to non-SOT recipients.\(^3,4\) COVID—19 leads to a high admission rate (80%-100%). Reported mortality rates in small series of lung transplantation (LTx) patients with COVID—19 range from 8% to 55%.\(^5—11\) Limited data are available regarding the transplant function outcome after COVID—19. In addition, single center studies have reported a significant association between COVID—19 and chronic lung allograft dysfunction (CLAD).\(^1—12\) The aim of this multicenter retrospective study was to evaluate the effect of COVID—19 on the clinical course and lung function in LTx patients.

Material and methods

Patients

The study was waived by the respective Ethical Committees based on its retrospective nature (METc number 2021.283). The study complies with the International Society for Heart and Lung Transplantation (ISHLT) Ethics Statement. All patients provided written informed consent upon entry into the program. Data were retrospectively collected at 3 transplant centers in the Netherlands. All adult patients who underwent unilateral or bilateral lung transplantation with a polymerase chain reaction confirmed COVID—19 between February 27, 2020 and September 1, 2021 were eligible for inclusion.

Transplant care

Follow-up of all patients took place at least every 3 months for monitoring of transplant function. All patients received standard maintenance immunosuppression: tacrolimus, prednisolone and mycophenolate mophetil. Alternative immunosuppressants were cyclosporine, azathioprine, everolimus or sirolimus (Table 1). Post-transplantation prophylactic therapy included cotrimoxazole for pneumocystis pneumonia and valganciclovir (5 mg/kg once daily) for cytomegalovirus, depending on cytomegalovirus (mis) match.

Comorbidities and symptoms

For chronic kidney disease we use the Kidney Disease Improving Global Outcomes staging.\(^13\) Heart failure is defined according to the 2021 European Society of Cardiology guidelines. Upper respiratory tract symptoms include: sore throat, rhinorrhea, nasal congestion, smell or taste disturbances.

Virologic diagnostics

The indications for testing for SARS-CoV-2 virus in LTx patient in our cohort are: 1) fever, with or without symptoms of respiratory tract infection, for example, cough, dyspnoea, running nose, loss of sense of smell or taste; 2) close contact with a confirmed COVID—19 infected person. SARS-CoV-2 infection was defined as a positive polymerase chain reaction on a nasopharyngeal swab. Swabs were collected by municipal public health services or at the hospital.

Pulmonary function

Spirometry was performed pre-COVID—19 as part of standard care. Baseline lung function is computed as the mean of the best 2 postoperative FEV1 measurements, taken >3 weeks apart. Lung function pre-COVID—19 was taken at 6 and 3 to 0 months before infection. Follow-up measurements were performed at the routine visits of outpatients with COVID—19 or 2 to 4 weeks after discharge in patients that had been admitted for COVID—19. Second measurement took place 6 months after COVID—19. Mild lung function loss is defined as a ≤10% loss in this forced expiratory volume in 1 second (FEV1) or forced vital capacity (FVC) 3 months post-COVID—19 compared to pre-COVID—19, whereas a >10% loss in FEV1 or FVC 3 months post-COVID—19 compared to pre-infection is classified as severe infection.\(^14\)

Spirometry was performed according to American Thoracic Society/European Respiratory Society guidelines.\(^15\) The Global Lung Function Initiative Network reference values were used to express percentages of predicted values, the z-scores and the lower limit of normal. CLAD was defined as a persistent decline of 20% or more in FEV1 value from baseline value post transplantation, independent of a change in FVC, according to the most recent ISHLT criteria.\(^16\)

Statistical analysis

Normally distributed continuous variables are expressed as mean (standard error of mean or median (quartiles)) for non-normally
distributed variables. Mann–Whitney U-test and chi-squared test were used to compare patient characteristics between admitted and non-admitted patients. Paired-samples t-test was used for within-group analyses to compare FEV1 and FVC pre- and post-COVID-19. Analyses were carried out using IBM SPSS for Mac, version 24.0. A p-value of less than 0.05 was used as the cut-off for significance. Log-rank test and Kaplan-Meier survival curves were used to investigate relations between low-flow oxygen, high-flow nasal oxygen (HFNO), invasive ventilation use and survival.

Results

Patients

Seventy-four from a total of 754 LTx patients (10%) had a confirmed COVID-19 infection at all 3 transplant centers in the Netherlands, between March 2020 and September 1, 2021 (Figure 1). The median follow-up period was 6 months (interquartile range (IQR) 5-8). Baseline characteristics for all LTx patients with COVID-19 are shown in Table 1. The median age was 59 years (IQR 48-65) and the majority of patients (45/74; 61%) were male. Chronic obstructive pulmonary disease (29/74; 39%) or pulmonary fibrosis (21/74; 28%) were the most common indications for LTx, and a bilateral LTx was performed in 64/74 (87%). The most frequent reported comorbidities were chronic kidney disease, hypertension and diabetes mellitus. Seven patients (7/74; 10%) were vaccinated before SARS-CoV-2 infection (2 vaccines). None of the patients used oxygen therapy before SARS-CoV-2 infection. The symptoms most commonly reported in LTx patients with COVID-19 were fatigue (38/74; 51%), upper respiratory symptoms (33/74; 45%; that is, sore throat, rhinorrhea, nasal congestion, smell or taste disturbances, fever (31/74; 42%), cough (31/74; 42%), and dyspnoea (30/74; 41%). Thirty-two of 74 patients (43%) were not hospitalized and closely monitored with home spirometry and oximetry combined with telephone or video consultation by the transplant team to assess for clinical and/or respiratory worsening warranting hospital admission. Forty-two out of 74 patients (57%) were hospitalized, of whom 19/42 (45%) were admitted to the ICU (Figure 1). Criteria for hospitalization were: clinical symptoms of (upper) respiratory infection, fever, shortness of breath with or without oxygen

### Table 1  Baseline Characteristics of Lung Transplant Patients With COVID-19

| Variable                        | All patients | Hospitalized | Non-hospitalized | p-value<sup>a</sup> | Died | p-value<sup>b</sup> |
|---------------------------------|--------------|--------------|------------------|---------------------|------|---------------------|
| Recipients, n (%)               | 74 (100)     | 42 (57)      | 32 (43)          |                     |      |                     |
| Age, years                      | 59 (48-65)   | 63 (54-67)   | 54 (39-63)       | 0.010               | 63 (49-71) | 0.010               |
| Gender, male (%)                | 45 (61)      | 24 (57)      | 21 (66)          | 0.459               | 9 (60) | 0.943               |
| Non-Caucasian, n (%)            | 9 (12)       | 6 (14)       | 3 (9)            | 0.522               | 2 (13) | 0.876               |
| Transplant indication, n (%)    |              |              |                  |                     |      |                     |
| COPD                            | 29 (39)      | 18 (43)      | 11 (34)          |                     |      |                     |
| Fibrosis                        | 21 (28)      | 13 (31)      | 8 (25)           |                     |      |                     |
| Pulmonary hypertension          | 5 (7)        | 2 (5)        | 3 (9)            |                     |      |                     |
| Cystic fibrosis                 | 15 (20)      | 6 (14)       | 9 (28)           |                     |      |                     |
| Other                           | 4 (5)        | 3 (7)        | 1 (3)            |                     |      |                     |
| Bilateral LTx, n (%)            | 64 (87)      | 35 (83)      | 29 (91)          | 0.363               | 11 (73) | 0.095               |
| Time since transplant, years    | 5 (2-10)     | 6 (2-10)     | 5 (1-11)         | 0.477               | 8 (2-11) | 0.477               |
| Body mass index, kg/m<sup>2</sup>  | 26 (24-29)   | 28 (24-32)   | 25 (23-27)       | 0.036               | 27 (20-32) | 0.036               |
| Comorbidities, n (%)            |              |              |                  |                     |      |                     |
| Hypertension                    | 27 (37)      | 18 (43)      | 9 (28)           | 0.192               | 5 (33) | 0.776               |
| Dyslipidemia                    | 7 (10)       | 2 (6)        | 5 (16)           | 0.114               | 1 (7) | 0.679               |
| Diabetes Mellitus               | 25 (34)      | 20 (48)      | 5 (16)           | 0.004               | 11 (73) | 0.000               |
| Chronic kidney disease          | 45 (61)      | 30 (71)      | 15 (47)          | 0.032               | 13 (87) | 0.022               |
| Atrial fibrillation             | 3 (4)        | 2 (5)        | 1 (3)            | 0.724               | 0 (0) | 0.373               |
| Heart failure                   | 4 (5)        | 3 (7)        | 1 (3)            | 0.449               | 1 (7) | 0.809               |
| Immunosuppression, n (%)        |              |              |                  |                     |      |                     |
| Tacrolimus                      | 71 (96)      | 40 (95)      | 31 (97)          | 14 (93)             |      |                     |
| CYC                             | 2 (3)        | 1 (2)        | 1 (3)            | 0 (0)               |      |                     |
| AZA                             | 6 (8)        | 3 (9)        | 3 (9)            | 1 (7)               |      |                     |
| MMF                             | 65 (87)      | 37 (88)      | 28 (88)          | 12 (80)             |      |                     |
| mTORi                           | 8 (11)       | 6 (14)       | 2 (6)            | 4 (27)              |      |                     |
| COVID-19 vaccination, n (%)      | 7 (10)       | 5 (12)       | 2 (6)            | 0 (0)               |      |                     |

<sup>a</sup>p-value for the difference between hospitalized patients and non-hospitalized patients.

<sup>b</sup>p-value for the difference between survivors and non-survivors.

<sup>c</sup>The vaccine used was mRNA (Moderna).
requirement (peripheral oxygen saturation <92%). Hospitalized patients and patients who died, were older, had more often diabetes, chronic kidney disease or a higher BMI (Table 1). No other significant differences in comorbidities were found between hospitalized and non-hospitalized patients and between survivors and non-survivors (Table 1). Hospitalized patients more often had symptoms of dyspnoea and myalgia than non-hospitalized patients (Table 2). There were no significant differences in clinical characteristics and comorbidities between patients admitted to the ICU or the general ward. After discharge all patients were followed routinely in the outpatient clinic. After 6 months the majority (33/59) had persisting symptoms; that is, fatigue, shortness of breath or coughing. The timeline of lung transplant patients with COVID-19 is shown in Figure 2. The median time between transplantation and COVID-19 was 5 years (IQR 2-10 years), with a median 2-day delay between symptom onset and polymerase chain reaction test. The median interval from test to hospitalization was 6 days (IQR 3-8 days). The median length of hospital stay was 2 weeks (IQR 7-26 days) and the median time between admission and death was 24 days (19-46 days).

COVID-19 management and outcome in LTx patients

Thirty-four out of 74 patients (46%) did not require supplementary oxygen. The median length of hospital stay of those patients who did not receive supplementary oxygen, was 2 days (IQR 1-2). Twenty of the 42 (48%) hospitalized patients received low-flow oxygen, 5/42 (12%) patients received HFNO and 15/42 (36%) patients needed invasive mechanical ventilation (Table 2). Of the fifteen mechanically ventilated patients 9 (60%) were intubated because of HFNO failure. The mortality was 60% (9/15) among mechanically ventilated patients and 40% (2/5) in patients who received HFNO. The Kaplan-Meier curve of survival in lung transplant patients with no supplementary oxygen, low flow oxygen, HFNO and invasive ventilation is shown in Figure 3. Survival of patients without supplemental oxygen was better when compared to low-flow oxygen, HFNO and invasive ventilation (p < 0.001). Patients on low-flow oxygen had better survival than on invasive ventilation (p < 0.01), but was not different from patients on HFNO (p = 0.16). There was no significant difference in survival between patients on HFNO and invasive ventilation (p = 0.65).

One patient received extracorporeal membrane oxygenation support. Corticosteroid dose was increased in those patients with lower respiratory tract symptoms and/or lung function decline. Patients who were not admitted with mild symptoms did not receive an increased dose of steroids. Corticosteroids were increased in 42/74 (57%) patients, of whom 6/42 (14%) patients were treated at home and 36/42 (86%) were admitted. Additional treatment consisted of hydroxychloroquine (3/74; 4%), remdesivir (6/74; 8%), tocilizumab (13/74; 18%), convalescent plasma (8/74; 11%) or monoclonal antibodies (2/74; 3%). Dose reductions or discontinuation of antimetabolite treatment occurred among 38/74 (51%) of patients, in 6/74 (8%) calcineurin inhibitors were adjusted to lower trough levels (6-7 μg/l). In one patient the tacrolimus was temporarily stopped and, in another patient who used tacrolimus, sirolimus and prednisolone, the sirolimus was discontinued. The median

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**Figure 1** Flow diagram among lung transplant (LTx) patients. CLAD, chronic lung allograft dysfunction; HFNO, high-flow nasal oxygen; IMV, invasive mechanical ventilation; LTx, lung transplantation.
length of hospitalization was 18 days (IQR 8-29). The overall COVID-19 related mortality in the cohort was 13/74 (18%), 2/60 (3%) patients died due to another cause (metastatic breast cancer, progressive multifocal leukoencephalopathy). Twelve out of 19 ICU patients died (63%), 3 died on the general wards. They were found not eligible for

| Symptons, n (%) | All patients n = 74 | Hospitalized n = 42 | Non-hospitalized n = 32 | p-value\(^a\) | Died n = 15 | p-value\(^b\) |
|----------------|---------------------|---------------------|------------------------|----------------|------------|------------|
| Fatigue | 38 (51) | 18 (43) | 15 (47) | 0.434 | 8 (53) | 0.672 |
| Dyspnoea | 30 (41) | 21 (50) | 9 (28) | 0.047 | 5 (33) | 0.649 |
| Cough | 31 (42) | 18 (43) | 13 (41) | 0.779 | 5 (33) | 0.570 |
| Chest pain | 7 (10) | 4 (10) | 3 (9) | 0.956 | 1 (7) | 0.730 |
| Fever | 31 (42) | 19 (45) | 12 (38) | 0.448 | 5 (33) | 0.570 |
| Myalgia | 13 (18) | 4 (10) | 9 (28) | 0.042 | 2 (13) | 0.702 |
| Gastro-intestinal | 21 (28) | 14 (33) | 7 (22) | 0.250 | 7 (47) | 0.051 |
| Headache | 19 (26) | 11 (26) | 8 (25) | 0.860 | 2 (13) | 0.265 |
| Upper respiratory | 33 (45) | 15 (36) | 18 (56) | 0.094 | 4 (31) | 0.844 |
| Respiratory support | | | | | | |
| Ambient air | 34 (46) | 2 (5) | 32 (100) | 0 (0) | | |
| Low-flow oxygen | 20 (27) | 20 (48) | 0 (0) | 4 (27) | | |
| High-flow oxygen | 5 (7) | 5 (12) | 0 (0) | 2 (13) | | |
| IMV | 15 (20) | 15 (36) | 0 (0) | 9 (60) | | |
| Treatment COVID-19 | | | | | | |
| None | 31 (42) | 5 (12) | 26 (81) | 2 (13) | | |
| Corticosteroids | 42 (57) | 36 (86) | 6 (19) | 13 (87) | | |
| Hydroxychloroquine | 3 (4) | 3 (7) | 0 (0) | 1 (7) | | |
| Remdesivir | 6 (8) | 6 (14) | 0 (0) | 3 (2) | | |
| Tocilizumab | 13 (18) | 13 (31) | 0 (0) | 5 (33) | | |
| Convalescent plasma | 8 (11) | 8 (19) | 0 (0) | 2 (13) | | |
| Monoclonal antibodies | 2 (3) | 2 (5) | 0 (0) | 0 (0) | | |
| Immunosuppressive medication adjustment | | | | | | |
| AM discontinued/lower dose | 38 (51) | 30 (71) | 8 (25) | 10 (67) | | |
| AZA | 3 (4) | 1 (2) | 2 (6) | 0 (0) | | |
| MMF | 35 (47) | 29 (69) | 6 (19) | 10 (67) | | |
| CI discontinued | 1 (1) | 1 (3) | 0 (0) | 1 (7) | | |
| CI lower trough levels | 6 (8) | 6 (14) | 0 (0) | 5 (33) | | |
| mTORi discontinued | 1 (1) | 1 (2) | 0 (0) | 1 (7) | | |
| ICU admission, n (%) | 19 (26) | 19 (45) | 0 (0) | 12 (80) | | |
| Died, n (%) | | | | | | |
| COVID-19 related | 13 (18) | 13 (31) | 0 (0) | 13 (87) | | |
| Other cause of death | 2 (3) | 2 (5) | 0 (0) | 2 (13) | | |

\(^a\) p-value for the difference between hospitalized patients and non-hospitalized patients.

\(^b\) p-value for the difference between survivors and non-survivors.

| Table 3 | Transplant Function Pre- and Post-COVID-19 |
|-----------------------------------------------|------------------------------------------|
| Pre-COVID-19 | 3 months post-COVID-19 | p-value | 6 months post-COVID-19 | p-value |
| FEV1, liter | 2.55 ± 0.10 Δ | 2.41 ± 0.11 Δ | 0.001 | 2.47 ± 0.11 Δ | 0.021 |
| 40/55/3 months | 138 ± 39 ml/3 months | 3.35 ± 0.16 Δ 233 ± 45 ml/3 months | 0.001 | 3.35 ± 0.16 Δ 117 ± 45 ml/6 months | 0.012 |
| FVC, liter | 3.58 ± 0.14 19±61/3 months | 3.35 ± 0.15 Δ 233 ± 62 ml/3 months | 0.219 | 73 ± 0.02 | 0.833 |
| 86 ml ± 36 ml/6 months | | | | 26 ± 0.58 | 0.163 |
| FEV1/FVC ratio | 72 ± 0.02 | 73 ± 0.02 | | 73 ± 0.02 | |
| BMI, kg/m² | 26 ± 0.58 | 26 ± 0.58 | | 26 ± 0.58 | |

FEV1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; Δ = ml lung function decline of pre-COVID-19 infection.
Continuous variables are expressed as mean and standard error of mean (SEM).
intensive treatment on the ICU, because of comorbidities and deteriorating performance status pre-COVID-19. All non-hospitalized patients survived. None of the vaccinated patients died. In patients who survived 33/59 (56%) had persisting symptoms after COVID-19 infection.

Transplant function

In 58/74 (78%) patients post-COVID-19 spirometry at 3 months was available and in 48/74 (65%) patients spirometry was available at 6 months post-COVID-19. There was a significant decline in FEV1 ($\Delta$FEV1 138 ± 39 ml, $p = 0.001$) and in FVC ($\Delta$FVC 233 ± 74 ml, $p = 0.000$) at first follow-up within 3 months (Table 3). There was no decline in FEV1/FVC ratio (0.72 vs 0.73) after COVID-19. Even though FEV1 ($\Delta$FEV1 24 ± 38 ml) and FVC ($\Delta$FVC 100 ± 46 ml) improved between the first follow-up (within 3 months) to 6 months, FEV1 and FVC remained significantly lower than pre-COVID-19 values ($\Delta$FEV1 86 ml ± 36 ml, $p = 0.021$; $\Delta$FVC 117 ± 35 ml, $p = 0.012$). Mean FEV1/FVC ratio after 6 months remained

![Timeline of lung transplant patients with COVID-19. Variables are expresses as median (interquartile range).](image1)

![Kaplan-Meier curve of survival in lung transplant patients with no supplementary oxygen, low-flow oxygen, high-flow nasal oxygen and invasive ventilation.](image2)

| Patients at risk | Time in weeks | 0 | 20 | 40 | 60 | 80 | 100 |
|-----------------|---------------|---|----|----|----|----|-----|
| No supplemental oxygen | 34 | 33 | 24 | 6 | 2 | 1 |
| Low-flow oxygen | 19 | 14 | 12 | 5 | 5 | 2 |
| High-flow nasal oxygen | 5 | 3 | 2 | - | - | - |
| Invasive ventilation | 14 | 6 | 5 | - | - | - |
>0.70. **Figure 4** demonstrates the percentage of FEV1 and FVC decline from pre-COVID-19 at 3- and 6-months post-COVID-19. There was no difference in FEV1 decline between hospitalized and non-hospitalized patients (\( p = 0.473 \)). There was a trend toward a more severe FVC decline in hospitalized patients than in non-hospitalized patients (\( \Delta 208 \pm 75 \text{ ml} vs \Delta 40 \pm 49 \text{ ml}; p = 0.059 \)).

In our cohort 15/58 (26%) of the patients had a severe loss in FEV1 and 18/58 patients (31%) had a severe loss in FVC 3 months after COVID-19. Patients with increased corticosteroid dose had more often severe lung function loss compared to those without increased corticosteroids dose (for FEV1 \( p = 0.007 \); for FVC \( p < 0.001 \)). No significant differences, except from hypertension, in comorbidities and clinical characteristics were found between patients with mild and severe FEV1 or FVC loss (supplementary table 1).

Lung function pre-COVID-19 in the cohort was stable, that is, there was no significant difference between FEV1 and FVC measurements 6 and 3 months pre-COVID-19 (\( \Delta \text{FEV1} 40 \text{ ml} \pm 55 \text{ ml}, p = 0.469; \Delta \text{FVC} 19 \pm 61 \text{ ml}, p = 0.756 \)).

Pre-COVID-19 there were 21/74 (28%) patients with CLAD, 6 months post-COVID-19 there were 15/48 (20%) patients with CLAD and 15 patients died (**Figure 5**). Seven out of 18 (39%) patients with the bronchiolitis obliterans syndrome (BOS) phenotype died and 1 patient converted to the restrictive allograft syndrome (RAS) phenotype. There were 3 patients with new BOS and 4 patients with new RAS. Patients with RAS or BOS pre-COVID-19 who survived, remained stable. In patients with CLAD pre-COVID-19, mortality appeared higher than in patients without CLAD (33% vs 15%), but the difference was not statistically significant (\( p = 0.078 \)). Two of the 7 vaccinated patients had stable CLAD and 2 patients developed new CLAD.

**Radiology**

In patients with severe FVC decline, 17/18 (94%) showed persistent changes on the x-ray or Computed Tomography (CT)-scan after 3 months. In 16 of these 17 patients the extent of the radiologic abnormalities improved over 3 months. In patients with severe FEV1 decline 9/15 (60%) showed persisting but improvement of radiologic abnormalities on x-ray or CT. In patients without severe FVC decline 4/37 (11%) had no abnormalities on x-ray or CT and in patients without severe FEV1 decline 12/40 (30%) show abnormalities on x-ray or CT. In summary, patients with a significant decline in FVC (\( p < 0.001 \)) or FEV1 (\( p = 0.041 \)) had significantly more x-ray or CT abnormalities than patients with no severe FVC or FEV1 decline.

**Discussion**

In this Dutch multicenter study, in which we studied LTx patients with COVID-19 for a follow-up period of 6 months, we showed that the clinical course may vary. More than half of the LTx patients required hospitalization and nearly 40% were in need of mechanical ventilation. However, COVID-19 in LTx patients may also have a mild clinical course without need for hospitalization, but with close monitoring at home. The older LTx patients with multiple comorbidities were hospitalized. In the hospitalized LTx patients COVID-19 results in higher mortality rate compared to the non-hospitalized. In addition, we showed that lung function decline after COVID-19 gradually improves from 3 to 6 months post infection, but remained significantly lower and showed a restrictive pattern compared to pre-COVID-19 values. Patients with CLAD did not progress over time, but mortality appeared to be higher when compared to the non-CLAD patients.

The incidence of COVID-19 among LTx patients during the first 18 months of the global COVID-19 pandemic, was similar to the general Dutch population (10%), which is remarkable since LTx patients are at higher risk for life threatening infections. This might be attributed to the number of unreported cases in the general population and the engagement of the LTx patients to the advised measures; that is, social distancing and wearing a non-surgical mask.
Hospitalized vs non-hospitalized

The hospital admission rate in our study was high (57%), but markedly lower than in previous series on LTx patients with COVID-19 (84-100%).\textsuperscript{5,7,18} This difference in hospitalization rate might be explained by the low threshold for testing and the shorter average home-to-hospital distance in the Netherlands, allowing close patient monitoring. Adequate outpatient management of mild COVID-19 is feasible in non-SOT patient and was shown to avoid hospitalization.\textsuperscript{19,20} It is unknown whether this is feasible in LTx patients. Nevertheless, home monitoring of LTx patients was safe in the Dutch setting with home spirometry, close contact and a short distance between hospital and LTx patient. There were no deaths in this group.

Despite the lower admission rate, nearly half of the hospitalized LTx patients were admitted to the ICU requiring invasive mechanical ventilation, indicating more severe disease. The intubation rate in LTx patient is much higher than in the general population (20% vs 4-12%).\textsuperscript{21} Also, the mortality rates in mechanical ventilated patients and in patients who received HFNO are higher.
than in the general population: 60% vs 21% in mechanical ventilated patients, and 40% vs 15% in patients who received HFNO. This might be explained by the more severe course of COVID-19 disease seen in LTx patients due to the immunocompromised state and the significant comorbidities in LTx patients.22

In line with COVID-19 risk factors in the general population, LTx patients hospitalized, and patients who died, were older, had more often diabetes, chronic kidney disease and a higher BMI.23

Management

Although the higher risk of severe disease and mortality, the management strategy among patients with LTx and COVID-19 has been similar to the general population in the Netherlands. In LTx patients treatment regimens were based on scientific evidence from studies and experience in the general non transplant population with additional international expert opinion summarized in the ISHLT consensus guidelines.24 Since the study period covers the start of the pandemic up to September 2021 treatment regimens have changed due to new insights. Therefore, different treatment regimens were used in our study according to national and regional availability of specific drugs and consensus on treatment regimens.

The majority of LTx patients were on a triple immunosuppressive regimen with calcineurin inhibitors, steroids and antimetabolites. When infected with COVID-19, most patients received an increased dosage of steroids in the case of severe symptoms, the need of supplemental oxygen or a decline in home spirometry. Antimetabolites were discontinued or reduced, which is in line with the study by Verleden et al and Pereira et al.8,25 However, it remains unclear which immunosuppressive has to be reduced, discontinued or continued at lower trough levels, considering the importance of hyperinflammation in the pathogenesis of severe COVID-19. Therefore more research on the optimal regime is needed in LTx patients with COVID-19.

Outcome

The COVID-19 mortality in LTx patients in our study (20%) is comparable to an 8% to 39% mortality rate in previous reports on SOT patients and LTx patients.5–11 Kamp et al suggested that the limited respiratory reserve and the substantial CLAD prevalence might contribute to poor outcomes.26 This is supported by our data which showed that mortality among patients with CLAD was high (33%), and showed a trend towards significance when compared to the non-CLAD patients.

Lung function

There was a decline in lung function 3 and 6 months after COVID-19. This is in line with a recent study of Mohanka et al among 13 LTx patients with available post-COVID-19 lung function, with a median follow-up of 43.5 days. They showed that 6 patients had >10% loss in FVC or FEV1.12 Kamp et al demonstrated a decline in TLC but not in FEV1 in LTx patients 4 to 12 weeks after survived SARS-CoV-2 infection.26 However, the effect of COVID-19 on lung function at long-term follow-up is unknown. Therefore, this is the first multicenter study in LTx patients to show that lung function gradually improved from 3 to 6 months follow-up, but remained significantly lower compared to pre-COVID-19 values. This is in agreement with a long-term follow-up study in non-SOT patients with COVID-19, that showed that restrictive lung function significantly improved over time, but was not resolved by 6 months.27 Moreover, the more restrictive pattern demonstrated in these studies is in agreement with our results.19,21 This restrictive pattern may be explained by the destruction in alveolar structure and pulmonary interstitial fibrosis found by autopsies of COVID-19.28 It might be that patients with more severe FVC decline have more fibrosis on CT-scan post-COVID-19. In our cohort, patients with severe FVC or FEV1 decline had significantly more x-ray or CT abnormalities than patients with no severe FVC or FEV1 decline (p < 0.001 and p = 0.041 respectively). However, in most of these patients the extent of the radiologic abnormalities improved over 3 months. Therefore, it seems that patients with severe lung function decline, especially in FVC, have more radiological abnormalities on CT or x-ray, but like lung function decline, these abnormalities improved over time.

Future studies are needed to explore the relationship between FVC decline and radiological changes. Other explanations for a restrictive lung function pattern might be an increase in BMI or a reduction in muscle strength. However, BMI did not change in our population and unfortunately, we have no data on muscle strength. Muscle weakness is common after ICU admission. In our cohort only 7 patients had post-COVID-19 lung function measured after ICU admission. Therefore, in our cohort, FVC fall is less likely to be related to muscle strength. Furthermore, the decline in FVC gradually improved at 6 months post-COVID-19, but did not return to pre-COVID values, while there were no patients with permanent muscle weakness in our cohort.

The amount of lung function decline 6 months after COVID-19 is not severe, but still significant. In addition, the decline in lung function might be underestimated, since the patients who died did not have available post-COVID-19 spirometry results. Pre-COVID-19 the average decline per 3 months in FEV1 was 40 ± 55 ml and in FVC 19 ± 61 ml. Therefore, a FEV1 decline of 138 ml and FVC decline of 233 ml between pre-COVID-19 and 3 months post-COVID-19 is indeed much more than expected in our LTx population. In addition, 26% of the patients had a severe loss in FEV1 and 31% had a severe loss in FVC 3 months after COVID-19, which indicates that COVID-19 does have an important influence on lung function. Two LTx patients stand out in terms of their FEV1 decrease (ΔFEV1 1130 and 990 ml) as shown in Figure 4A. Both patients were male, 58 and 63 years, had a history of chronic obstructive pulmonary disease and obesity (BMI 28 and 31) without other
comorbidities and were using standard immunosuppression (tacrolimus, prednisolone and mycophenolate mofetil). One of the patients had a stenosis of the right main bronchus. Both had CLAD grade 0 before COVID-19. Those 2 patients were not hospitalized and did not use supplementary oxygen. Only steroids were increased. In addition to age and BMI, there were no other parameters who could predict such severe lung function decline due to COVID-19.

Post infection improvement in pulmonary function has been demonstrated in non-SOT and LTx patients with non-SARS-CoV-2 viral infections. De Zwart et al showed that in LTx patients with non-COVID-19 viral infections, only 17% did not return to their pre infection FEV1-value at 6 months post infection. Long term follow-up needs to be awaited whether lung function in LTx patients post-COVID-19 infection may recover completely.

After COVID-19, patients with CLAD did not progress over time in this study. Our findings are conflicting with the study by Kamp et al. They showed that in the subgroup of LTx recipients with pre-existing CLAD 43% had a substantial deterioration in graft function at 4 to 12 weeks post-COVID-19 infection. Although there were no cases of progressive CLAD in our study, 33% of the patients with CLAD died. The lung function post-COVID-19 of these patients was unknown. This difference in the number of patients with CLAD progression, might also be explained by the longer follow-up period in our study. There were 3 patients with new BOS and 4 with new RAS (1 conversion from BOS to RAS). Several studies have shown the effect of non-COVID-19 respiratory virus infections on the incidence of CLAD. In these studies, a restrictive pattern was less common than an obstructive pattern, which does not correspond to the more restrictive pattern seen after COVID-19 in our study. Our findings are in line with the study of Mahan et al who showed that the 3 patients with CLAD post-COVID-19, all had RAS phenotype.

Our study has some limitations. First, not all patients had available follow-up spirometry results. Second, due to evolving insights over the past 18 months, patient management has been diverse, which may have affected the clinical course and outcome. Administration of vaccines might also be explained by the longer follow-up period in our study. There were 3 patients with new BOS and 4 with new RAS (1 conversion from BOS to RAS). Several studies have shown the effect of non-COVID-19 respiratory virus infections on the incidence of CLAD. In these studies, a restrictive pattern was less common than an obstructive pattern, which does not correspond to the more restrictive pattern seen after COVID-19 in our study. Our findings are in line with the study of Mahan et al who showed that the 3 patients with CLAD post-COVID-19, all had RAS phenotype. In these studies, a restrictive pattern was less common than an obstructive pattern, which does not correspond to the more restrictive pattern seen after COVID-19 in our study.

In conclusion, COVID-19 infection in LTx patients results in high hospitalization and mortality rate. There was a decline in lung function shortly after infection which gradually improved at 6 months post-COVID-19, but did not return to pre-COVID-19 values and showed a more restrictive pattern. Patients with CLAD did not progress over time, but mortality appeared to be higher when compared to the non-CLAD patients.

Author contributions
A.G., C.G. and E.R. designed the study and wrote the manuscript. A.G., B.L., E.B., E.R. and M.H. collected the data. A.G. performed the statistical analyses. The figures and tables were designed by A.G. and E.R. All authors provided critical feedback and contributed to the revising of the manuscript.

Disclosure statement
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Supplementary materials
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References
1. World Health Organization. 55th ed. COVID-19 Weekly Epidemiological Update. Geneva, Switzerland: World Health Organization; 2021.

2. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of Coronavirus Disease 2019 (COVID-19): a review. JAMA 2020;324:782-93.

3. Fisher CE, Preiksaitis CM, Lease ED, et al. Symptomatic respiratory virus infection and chronic lung allograft dysfunction. Clin Infect Dis 2016;62:313-9.

4. Heldman MR, Kates OS, Safa K. COVID-19 in hospitalized lung and non-lung solid organ transplant recipients: a comparative analysis from a multicenter study. Am J Transpl 2021;21:2774-84.

5. Myers CN, Scott JH, Criner GJ, et al. COVID-19 in lung transplant recipients. Transplant Infect Dis 2020;22:e13364.

6. Aversa M, Benvenuto L, Anderson M. COVID-19 in lung transplant recipients: a single center case series from New York City. Am J Transpl 2020;20:3072-80.

7. Permpalung N, Bazemore K, Chiang TP-Y, et al. Impact of COVID-19 on lung allograft and clinical outcomes in lung transplant recipients: a case-control study. Transplantation 2021;105:2072-9.

8. Verleden GM, Godinas L, Lorent N. COVID-19 in lung transplant patients: a case series. Am J Transpl 2020;20:3234-8.

9. Messika J, Eloy P, Roux A, et al. COVID-19 in lung transplant recipients. Transplantation 2021;105:177-86.

10. Amor SM, Fox BD, Grubstein A, et al. Poor outcomes of COVID-19 in lung transplant recipients. Cohort study in a single center. J Heart Lung Transplant 2021;40:S144.

11. Legeai C, Cantrelle C, Jasseron C, et al. Death rate in lung transplant recipients during the COVID-19 outbreak in France. J Heart Lung Transplant 2021;40:S143.

12. Mohanka MR, Mahan LD, Joens J, et al. Clinical characteristics, management practices, and outcomes among lung transplant patients with COVID-19. J Heart Lung Transplant 2021;40:936-47.

13. Stevens PE. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013;158:825-30.
14. de Zwart AES, Riezebos-Brilman A, Alfenaar JWC, et al. Evaluation of 10 years of parainfluenza virus, human metapneumovirus, and respiratory syncytial virus infections in lung transplant recipients. Am J Transpl 2020;20:3529-37.

15. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.

16. Verleden GM, Glanville AR, Lease ED, et al. Chronic lung allograft dysfunction: definition, diagnostic criteria, and approaches to treatment - a consensus report from the pulmonary council of the ISHLT. J Heart Lung Transpl 2019;38:493-503.

17. RIVM. Actuele cijfers en trends covid19 in Nederland en wereldwijd. https://www.databronncovid19.nl/Bron?naam=Actuele-cijfers-en-trends-covid19-in-Nederland-en-wereldwijd. Retrieved October 28, 2021.

18. Saez-Giménez B, Berastegui C, Barrecheguren M, et al. COVID-19 in lung transplant recipients: a multicenter study. Am J Transpl 2021;21:1816-24.

19. Chevallier Lugon C, Smit M, Salamun J, et al. Novel outpatient management of mild to moderate COVID-19 spares hospital capacity and safeguards patient outcome: the Geneva pneumoCoV-Ambu study. PloS ONE 2021;16:e0247774.

20. Fisher AM, Schlauch D, Mulloy M, et al. Outcomes of COVID-19 in hospitalized solid organ transplant recipients compared to a matched cohort of non-transplant patients at a national healthcare system in the United States. Clin Transplant 2021;35:e14216.

21. Nishikimi M, Rasul R, Sison CP, et al. Intubated COVID-19 predictive (ICOP) score for early mortality after intubation in patients with COVID-19. Sci Rep 2021;11:21124.

22. Mellado-Artigas R, Ferreyro BL, Angriamn F, et al. High-flow nasal oxygen in patients with COVID-19-associated acute respiratory failure. Critical Care 2021;25:58.

23. Clark A, Jit M, Warren-Gash C, et al. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. Lancet Global Health 2020;8:e1003-17.

24. ISHLT Covid-19 Task Force. Guidance from the international society of heart and lung transplantation regarding the SARS CoV-2 pandemic. https://ishlt.org/ishlt/media/documents/SARS-CoV-2-Guidance-for-Cardiothoracic-Transplant-and-VAD-centers.pdfversion; Retrieved September 24, 2020.

25. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter. Am J Transpl 2020;20:1800-8.

26. Kamp JC, Hinrichs JB, Fuge J, Ewen R, Gottlieb J. COVID-19 in lung transplant recipients-risk prediction and outcomes. PloS one 2021;16:e0257807.

27. Stylemans D, Smet J, Hanon S. Evolution of lung function and chest CT 6 months after COVID-19 pneumonia: real-life data from a Belgian university hospital. Respir Med 2021;182:106421.

28. Yao XH, Li TY, He ZC, et al. [A pathological report of three COVID-19 cases by minimal invasive autopsies]. Zhonghua Bing Li Xue Za Zhi = Chinese J Pathol 2020;49:411-9.

29. Peghin M, Los-Arcos I, Hirsch HH, et al. Community-acquired respiratory viruses are a risk factor for chronic lung allograft dysfunction. Clin Infect Dis 2019;69:1192-7.

30. Allyn PR, Duffy EL, Humphries RM, et al. Graft loss and CLAD-onset is hastened by viral pneumonia after lung transplantation. Transplantation 2016;100:2424-31.

31. Mahan LD, Lill I, Halverson Q, et al. Post-infection pulmonary sequelae after COVID-19 among patients with lung transplantation. Transpl Infect Dis 2021;23:e13739.