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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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KEYWORDS:

COVID-19;
SARS-CoV-2;
lung transplant;
CLAD;
transplant function

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) (Δ FEV1 138 ± 39 ml, $p = 0.001$), and forced vital capacity (FVC) (Δ FVC 233 ± 74 ml, $p = 0.000$) 3 months post infection. Lung function improved slightly from 3 to 6 months after COVID-19 (Δ FEV1 24 ± 38 ml; Δ FVC 100 ± 46 ml), but remained significantly lower than pre-COVID-19 values (Δ FEV1 86 ml ± 36 ml, $p = 0.021$; Δ FVC 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

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Abbreviations: AM, antimetabolite; BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HFO, high-flow oxygen; ICU, intensive care unit; ILD, interstitial lung disease; LTx, lung transplant/lung transplantation; mTORi, mammalian target of rapamycin inhibitors; RAS,

restrictive allograft syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SOT, solid organ transplant

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significantly lower compared to pre-COVID-19 values. The more significant decline in FVC than in FEV1 and FEV1/FVC > 70%, suggested a more restrictive pattern.

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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).^{4,12} 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

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

Variable	All patients	Hospitalized	Non-hospitalized	<i>p</i> -value ^a	Died	<i>p</i> -value ^b
Recipients, <i>n</i> (%)	74 (100)	42 (57)	32 (43)		15 (20)	
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, <i>n</i> (%)	9 (12)	6 (14)	3 (9)	0.522	2 (13)	0.876
Transplant indication, <i>n</i> (%)						
COPD	29 (39)	18 (43)	11 (34)		9 (60)	
Fibrosis	21 (28)	13 (31)	8 (25)		2 (13)	
Pulmonary hypertension	5 (7)	2 (5)	3 (9)		0 (0)	
Cystic fibrosis	15 (20)	6 (14)	9 (28)		3 (20)	
Other	4 (5)	3 (7)	1 (3)		1 (6)	
Bilateral LTx, <i>n</i> (%)	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 ²	26 (24-29)	28 (24-32)	25 (23-27)	0.036	27 (20-32)	0.036
Comorbidities, <i>n</i> (%)						
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, <i>n</i> (%)						
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, <i>n</i> (%) ^c	7 (10)	5 (12)	2 (6)		0 (0)	

AZA, azathioprine; COPD, chronic obstructive pulmonary disease; CYC, cyclosporine; LTx, lung transplantation; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitors (everolimus or sirolimus).

Continuous variables are expressed as median (interquartile range).

^a*p*-value for the difference between hospitalized patients and non-hospitalized patients.

^b*p*-value for the difference between survivors and non-survivors.

^cThe vaccine used was mRNA (Moderna).

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

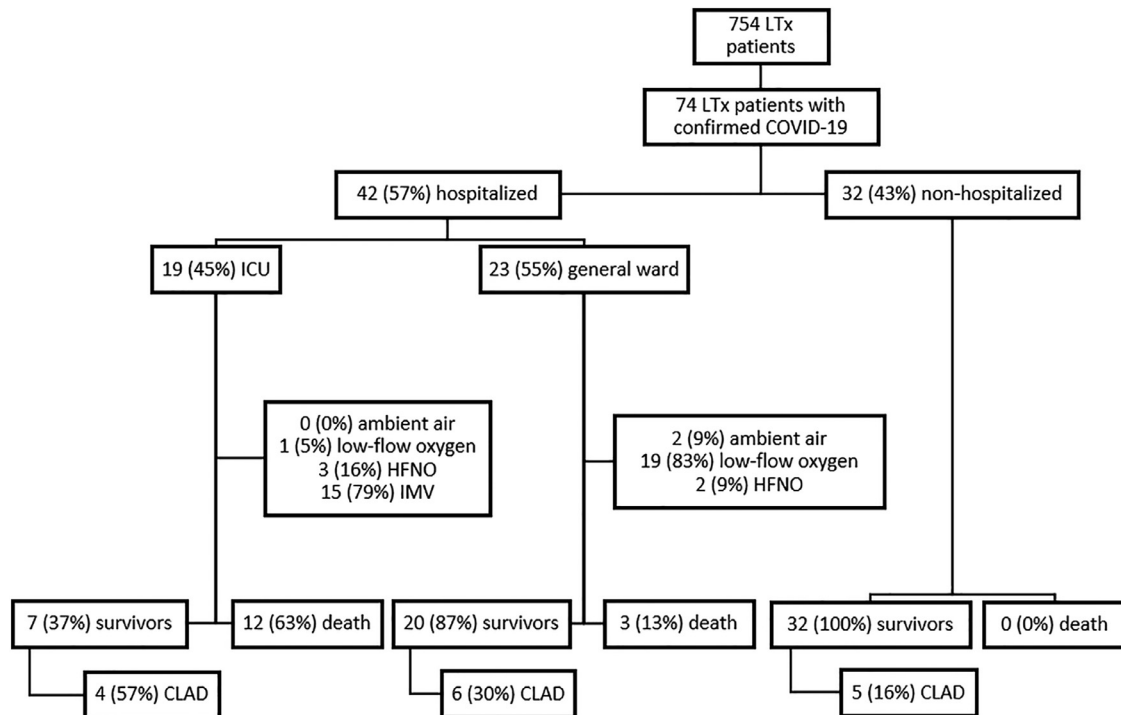


Figure 1 Flow diagram among lung transplant (LTx) patients. CLAD, chronic lung allograft dysfunction; HFNO, high-flow nasal oxygen; IMV, invasive mechanical ventilation; LTx, lung transplantation.

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 $\mu\text{mg/l}$). In one patient the tacrolimus was temporarily stopped and, in another patient who used tacrolimus, sirolimus and prednisolone, the sirolimus was discontinued. The median

Table 2 Clinical Data Lung Transplant Patients With COVID-19

	All patients <i>n</i> = 74	Hospitalized <i>n</i> = 42	Non-hospitalized <i>n</i> = 32	<i>p</i> -value ^a	Died <i>n</i> = 15	<i>p</i> -value ^b
Symptoms, <i>n</i> (%)						
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, <i>n</i> (%)	19 (26)	19 (45)	0 (0)		12 (80)	
Died, <i>n</i> (%)						
COVID-19 related	13 (18)	13 (31)	0 (0)		13 (87)	
Other cause of death	2 (3)	2 (5)	0 (0)		2 (13)	

AM, antimetabolite; AZA, azathioprine; CI, calcineurin inhibitor; ICU, intensive care unit; IMV, invasive mechanical ventilation; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitors.

Continuous variables are expressed as median (interquartile range).

^a*p*-value for the difference between hospitalized patients and non-hospitalized patients.

^b*p*-value for the difference between survivors and non-survivors.

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

Table 3 Transplant Function Pre- and Post-COVID-19

	Pre-COVID-19	3 months post-COVID-19	<i>p</i> -value	6 months post-COVID-19	<i>p</i> -value
FEV1, liter	2.55 ± 0.10 Δ 40 ± 55/3 months	2.41 ± 0.11 Δ 138 ± 39 ml/3 months	0.001	2.47 ± 0.11 Δ 86 ml ± 36 ml/6 months	0.021
FVC, liter	3.58 ± 0.14 19 ± 61/3 months	3.35 ± 0.15 Δ 233 ± 62 ml/3 months	0.001	3.35 ± 0.16 Δ 117 ± 45 ml/6 months	0.012
FEV1/FVC ratio	72 ± 0.02	73 ± 0.02	0.219	73 ± 0.02	0.833
BMI, kg/m ²	26 ± 0.58			26 ± 0.58	0.163

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).

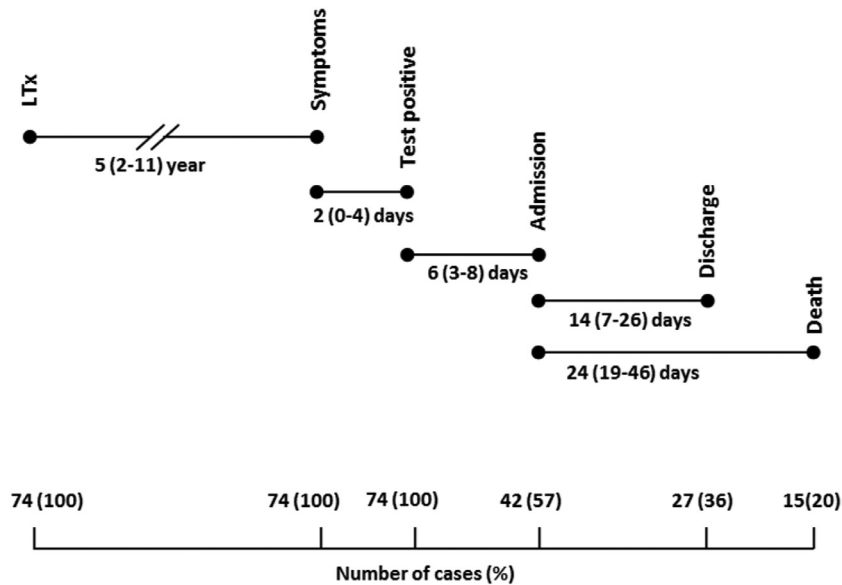


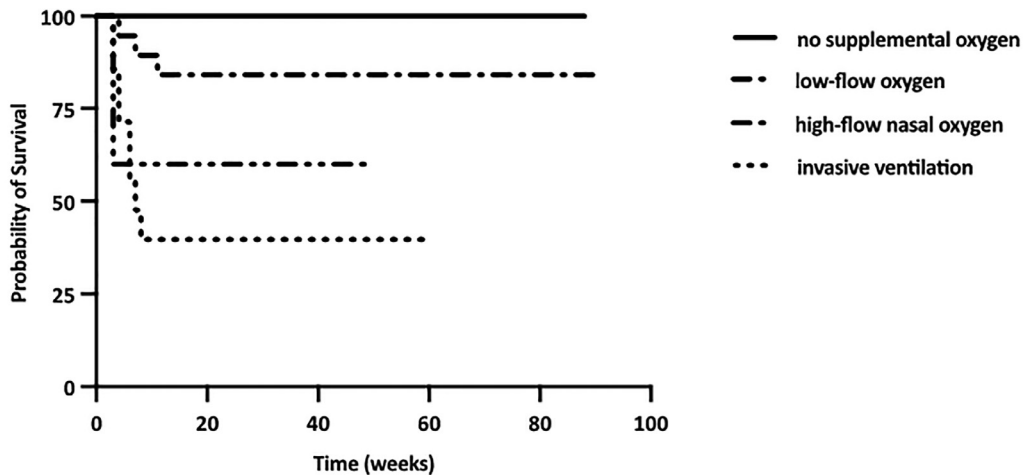
Figure 2 Timeline of lung transplant patients with COVID-19. Variables are expressed as median (interquartile range).

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 (Δ FEV1 138 ± 39 ml, $p = 0.001$) and in FVC (Δ 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 (Δ FEV1 24 ± 38 ml) and FVC (Δ 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 (Δ FEV1 86 ml ± 36 ml, $p = 0.021$; Δ FVC 117 ± 35 ml, $p = 0.012$). Mean FEV1/FVC ratio after 6 months remained



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	-	-	-

Figure 3 Kaplan-Meier curve of survival in lung transplant patients with no supplementary oxygen, low-flow oxygen, high-flow nasal oxygen and invasive ventilation.

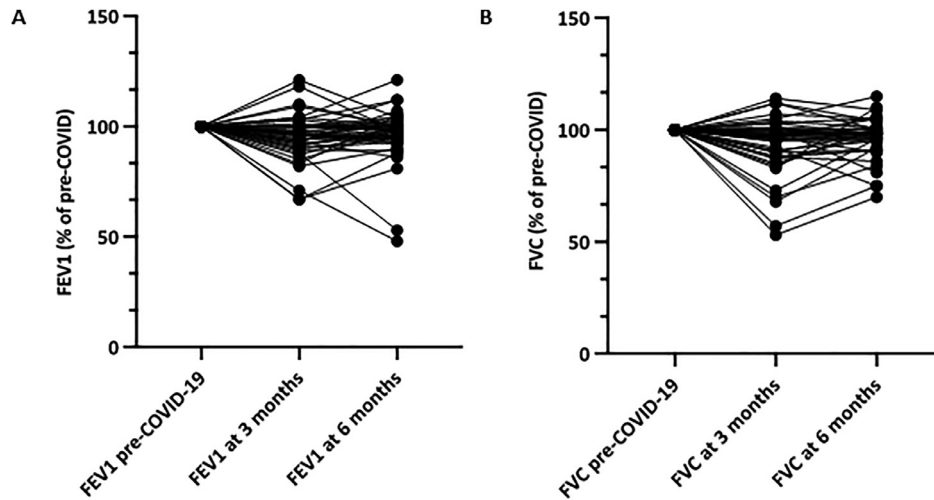


Figure 4 (A) FEV1 and (B) FVC decline 3 and 6 months post-COVID-19 in lung transplant patients with available spirometry 6 months post-COVID-19. FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

>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 ($\Delta 208 \pm 75$ ml vs $\Delta 40 \pm 49$ 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 (Δ FEV1 40 ml \pm 55 ml, $p = 0.469$; Δ FVC 19 \pm 61 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%),¹⁷ 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.

Pre-COVID-19

6 months post-COVID-19

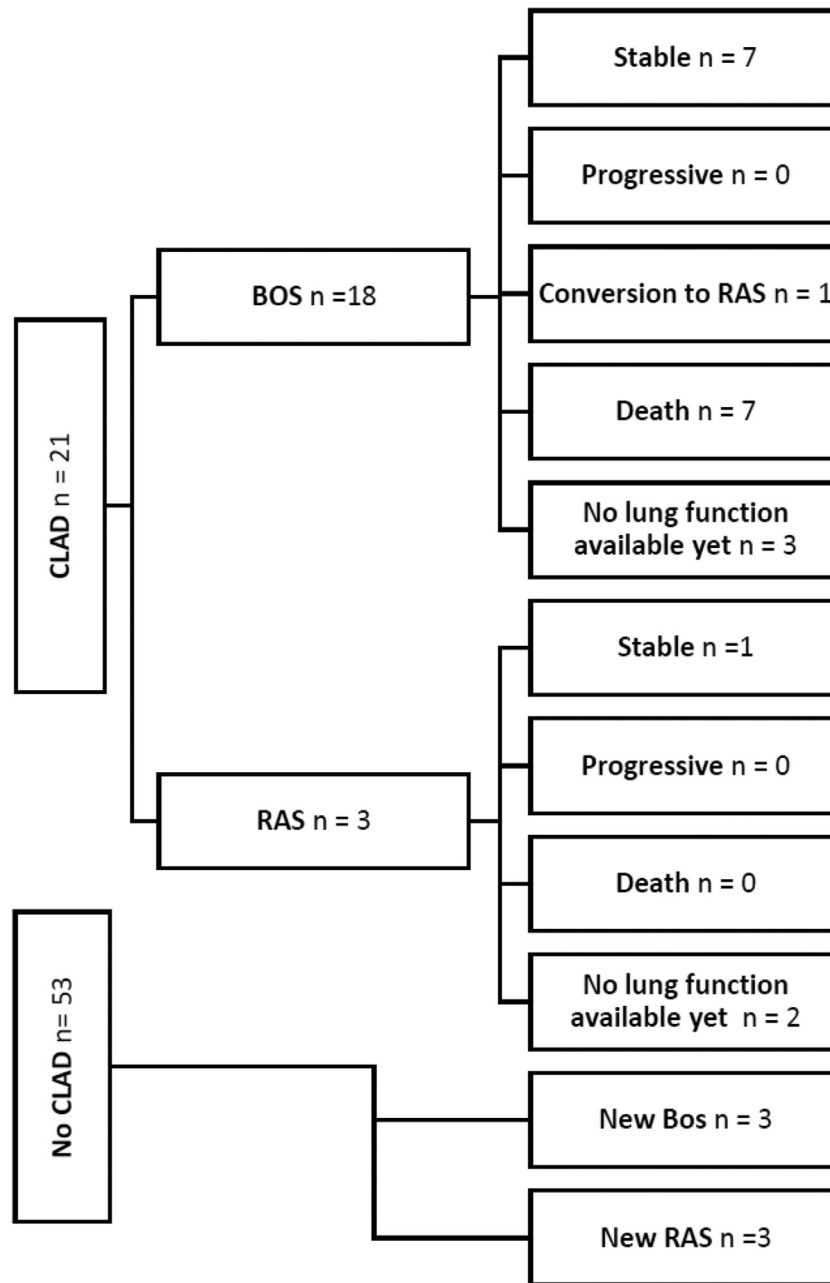


Figure 5 CLAD incidence pre-COVID-19 and 6 months post-COVID-19. BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; RAS, restrictive allograft syndrome.

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%).^{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.^{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%).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 (Δ FEV1 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.²⁶ 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.^{14,29,30} 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.³¹

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 have an effect on the clinical course. Third, we did not have a matched control group to compare transplant function over time. Fourth, to fulfil the definition of RAS, according to Verleden et al, TLC is needed.¹⁶ Unfortunately, we did not have TLC results in the majority of our patients. Therefore, the findings of a restrictive pattern in lung function should be interpreted with caution.

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

The authors of this manuscript have no conflicts of interest to disclose as described by the Journal of Heart and Lung Transplantation.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.hclun.2022.06.011>.

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