

ORIGINAL ARTICLE

COVID-19 in lung transplant recipients: an overview of the Swedish national experience

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SUMMARY

Although it is known that solid organ transplant recipients fare worse after COVID-19 infection, data on the impact of COVID-19 on clinical outcomes and allograft function in lung transplant (LTx) recipients are limited and based mainly on reports with short follow-up. In this nationwide study, all LTx recipients with COVID-19 diagnosed from 1 February 2020 to 30 April 2021 were included. The patients were followed until 1 August 2021 or death. We analysed demographics, clinical features, therapeutic management and outcomes, including lung function. Forty-seven patients were identified: median age was 59 (10–78) years, 53.1% were male, and median follow-up was 194 (23–509) days. COVID-19 was asymptomatic or mild at presentation in 48.9%. Nine patients (19.1%) were vaccinated pre-COVID infection. Two patients (4.3%) died within 28 days of testing positive, and the overall survival rate was 85.1%. The patients with asymptomatic or mild symptoms had a higher median % expected forced expiratory volume during the first second than the patients with worse symptoms ($P = 0.004$). LTx recipients develop the entire spectrum of COVID-19, and in addition to previously acknowledged risk factors, lower pre-COVID lung function was associated with more severe disease presentation.

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Key words

COVID-19, lung function, lung transplantation, multicentre study, severity, survival

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Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease ranging from asymptomatic and mild forms to lethal forms evolving with acute respiratory distress syndrome, sepsis or multisystem organ dysfunction [1]. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has an affinity to infect airway cells [2]. Typical features of COVID-19 are the destruction of the alveolar epithelium, hyaline membrane formation, capillary damage and pulmonary consolidation [3]. The ensuing alveolar septal fibroproliferation may evolve towards chronic vascular and alveolar remodelling leading to lung fibrosis and pulmonary hypertension. These findings generate concerns regarding the long-term effects of COVID-19 infection on pulmonary function.

Lung transplant (LTx) recipients are perceived as a high-risk patient group for COVID-19 because of the respiratory nature of their condition and the reduced ability to fight infections. Moreover, the transplanted lungs may suffer from the consequences of ischaemia–reperfusion injury or the recipient's immune response. Several reports have found that LTx recipients have the highest mortality among solid organ recipients infected with COVID-19, suggesting particular risk factors in this patient group [4,5]. However, detailed analyses of LTx recipients and long-term follow-up are still scarce. Furthermore, most published literature focuses mainly on hospitalized patients, and reports on LTx recipients developing COVID-19 managed as outpatients are largely missing [6–10].

Sweden is a country where the healthcare system is divided into 21 regional governing boards with a mandate to establish local clinical routines and practices. Because of the high degree of regional autonomy, the national health authorities manage health care through general recommendations rather than direct interventions. During the pandemic, the Swedish policy for tackling the pandemic stood out internationally, with no mandatory lockdowns and fewer obligatory restrictions. In addition, hydroxychloroquine was never recommended as part of the COVID-19 treatment. The transplant population was initially instructed to follow the general societal recommendations based on age rather than other risk factors. Therefore, it can be expected that COVID-19 was more common among organ transplant recipients in Sweden than in countries with a stricter approach to managing the pandemic.

In the current study, we collected data from all LTx patients with COVID-19 who had been in contact with

one of the two Swedish lung transplant centres in Gothenburg and Lund, regardless of the severity of infection. We aimed to describe the clinical course, management and outcome of LTx recipients with COVID-19 in Sweden. We assessed the impact of disease severity at presentation on the clinical course, including pulmonary function post-COVID and identified factors associated with worse severity of the disease.

Patients and methods

This national retrospective cohort study included all LTx recipients in Sweden who tested positive for SARS-CoV-2 polymerase chain reaction (PCR) between 1 February 2020 and 30 April 2021, at any place in Sweden. The indication for testing was presenting one or more symptoms associated with COVID-19 or as part of infection tracing. A nasopharyngeal swab was used for the first positive sample in all cases.

All referring hospitals were instructed to report to one of the two transplant centres whenever an LTx recipient was admitted. Furthermore, all lung transplant recipients were asked to contact their respective transplant centre upon receiving word of a positive test, regardless of symptomatology. All tests were analysed at the laboratory associated with the respective testing site, with the methodology used at that laboratory. All included patients were followed until death or 1 August 2021.

Patient information was retrieved through a review of electronic patient records. National Early Warning Score (NEWS) 2 score at contact was used for assessing acute illness on presentation. NEWS2 includes respiratory rate, oxygen saturation, need for supplemental oxygen, body temperature, blood pressure, heart rate and consciousness. COVID-19 Treatment Guidelines Panel National Institutes of Health [11] was used to classify the severity at presentation as asymptomatic, mild, moderate, severe or critical, as presented in Table 1. Comorbidities were reported according to Charlson's comorbidity index (CCI) [12]. Kidney function was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation. The most recent kidney function before SARS-CoV-2 infection was used as the baseline. In addition, all applied specific therapies with the intent to treat COVID-19 and vaccination status preinfection were recorded.

Vaccination data were obtained by medical journal review and from the vaccination registry.

All available initial radiological images were collected to Sahlgrenska University hospital and re-examined by a

Table 1. NIH Classification of COVID-19 illness severity.

Asymptomatic	Positive for SARS-CoV-2 at a virology test (i.e. PCR or antigen test) but without symptoms consistent with COVID-19.
Mild disease	Various signs and symptoms of COVID-19 (i.e. fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell) but without shortness of breath, dyspnoea or abnormal chest imaging.
Moderate disease	Evidence of lower respiratory disease during clinical assessment (dyspnoea) or imaging and who have an SpO ₂ ≥94% on room air at sea level.
Severe disease	SpO ₂ <94% on room air at sea level, a ratio of PaO ₂ /FiO ₂ <300 mm Hg, respiratory frequency >30 breaths/min or lung infiltrates >50%.
Critical disease	Respiratory failure, septic shock and/or multiple organ dysfunction.

Reference: <https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/>

NIH, National Institutes of Health; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction; SpO₂, oxygen saturation; PaO₂/FiO₂, arterial partial pressure of oxygen to fraction of inspired oxygen.

senior radiologist with extensive COVID-19 experience. The radiologist was blinded to the severity and timing of the examinations. All findings were classified according to the British Society of Thoracic Imaging (BSTI) [13]. The BSTI standard was chosen based on operator familiarity. Furthermore, all CTs were reanalysed for the occurrence of thromboembolism.

Routine dynamic follow-up spirometry was performed at the follow-up site closest to the patient during the pandemic. Three months after the start of the first wave of COVID-19, new guidelines were issued, recommending extra follow-up dynamic pulmonary function tests (PFT) during the first three months after the primary infection, regardless of severity. After the three initial months, follow-up spirometries were performed at the discretion of the referring doctor, with no more than six months between spirometries. The PFTs included in this study were performed according to the European Respiratory Society's standards [14], at least three weeks apart. Sequential follow-up spirometries were collected and divided into three time periods depending on when they were performed (0–30, 31–90 and 91–280 days after COVID-19 diagnosis). The best spirometry provided per patient within each period was included. The difference between the last spirometry before COVID-19 and post-COVID spirometries was recorded as Δ FEV1.

Patients were divided into two groups by COVID-19 severity. The groups were asymptomatic or mild disease vs moderate or worse. Standard immunosuppressive treatment protocol and prophylaxis protocols are provided as the supplementary information (S1). The administration of four immunosuppressive drugs in parallel was defined as quadruple therapy, three drugs

in parallel as triple therapy and two drugs as dual therapy.

Chronic lung allograft dysfunction (CLAD) was defined according to the current guidelines [15] by the attending lung transplant pulmonologist.

The study was conducted per the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and reviewed and approved by the Swedish Ethical Review Authority (#2020-04323). The Swedish Ethical Review Authority waived the requirement for informed consent for the study.

Statistics

Data are shown as median and range or as absolute and relative frequencies as appropriate. Categorical variables were compared using the Fisher exact test, and continuous variables were compared using the Mann–Whitney *U*-test. The Kaplan–Meier test and the log-rank test were used to compare survival. Potential risk factors for death were analysed using univariate Cox regression. Analyses were performed using GraphPad Prism v. 6 (GraphPad Software, San Diego, CA, USA) and SAS 9.4 statistical software (SAS Institute, Cary, NC, USA). A *P*-value < 0.05 was considered significant.

Results

Patients

Five hundred and twenty-four LTx recipients were alive in Sweden on 1 January 2020. In addition, 68 LTx were performed until 30 April 2021, resulting in 592 patients at risk. Forty-seven LTx infected with SARS-CoV-2 were

identified within the defined period, resulting in a cumulative incidence of 7.9%. Among the patients transplanted before the pandemic, 39 out of 524 (7.4%) tested positive. Among the patients transplanted during the pandemic, 8 out of 68 (11.7%) tested positive. This difference was not statistically significant [$P = 0.25$]. Patient characteristics are described in Table 2. The median age of the patients was 59 (10–78), and the most common comorbidities were hypertension in 19 patients (40.4%) and diabetes in 14 (29.7%) patients. A CCI of 1–2 was found in 26 (55.3) of the LTx recipients, eight patients (17%) had a CCI of 3–4, while eight (17%) had an index of ≥ 5 .

Clinical presentation, initial disease dynamics and patient management

Twenty-two patients (46.8%) presented with mild disease, and one (2.1%) was asymptomatic (detected because of infection tracing). Twenty LTx recipients (42.5%) developed moderate or severe COVID-19, whereas four patients (8.5%) presented with critical disease. Four patients sought advice by telephone or otherwise before the time of testing. No patient presenting with mild disease at PCR testing and subsequently treated as an outpatient returned with worsening symptoms within 28 days. Nine out of 21 (42.8%) patients presenting as moderate or severe progressed in disease severity during the initial admission. Among the four patients admitted in critical condition, one patient recovered and was discharged from the hospital.

Twenty-nine patients (61.7%) were hospitalized, whereas eighteen patients (38.3%) were treated entirely as outpatients (Table 2). When comparing patients according to disease severity, patients with moderate/severe symptoms compared with mild/asymptomatic disease had a higher median age [61 (51–78) vs. 51 (10–73) ($P = 0.006$)], a higher body mass index (BMI) [27.8 (22.0–39.9) vs. 22.8 (14.0–33.0) vs. ($P = 0.003$)] and a lower baseline estimated glomerular filtration rate (eGFR) [49.6 (6–93.3) vs. 68.7(29.4–185.3) ($P < 0.010$)]. Furthermore, cyclosporine treatment was more frequent in patients presenting with worse symptoms, as opposed to tacrolimus treatment [16(69.6%) vs. 8 (33.3%) ($P = 0.02$)]. Also, patients with asymptomatic or mild symptoms had a higher median % expected forced expiratory volume during the first second (FEV1) than the patients with worse symptoms [79 (36–106) vs. 57 (21–100)] ($P = 0.004$) and single LTx recipients were less common [0 (0) vs. 5 (20.8) ($P = 0.049$)] (Table 3).

Table 2. Patient baseline data, COVID-19 management and outcome.

	All patients ($n = 47$)
Males (%)	25 (53.1)
Age, median (range)	59 (10–78)
Months since transplant, median (range)	58 (1–246)
First year after transplant (%)	8 (17.0)
Baseline eGFR ml/min/1.73 m ² , median (range)	60.6 (10.0–180)
Body mass index kg/m ² , median (range)	26 (14.0–39.9)
Type of transplant and re-transplants, n (%)	
Single lung	5 (10.6)
Double lung	41 (87.2)
Heart–lung	1 (2.1)
Re-transplant	4 (8.5)
CCI (%)	
CCI 0	5 (10.6)
CCI 1 or 2	26 (55.3)
CCI 3 or 4	8 (17.0)
CCI ≥ 5	8 (17.0)
Comorbidities, n (%)	
Hypertension	19 (40.4)
Diabetes	14 (29.7)
Cardiovascular	6 (12.2)
Malignancy	5 (10.6)
Obesity (BMI ≥ 30 kg/m ²)	9 (19.1)
CKD stages 4–5	5 (10.6)
Chronic lung allograft dysfunction (CLAD), n (%)	
CLAD any severity	17 (36.2)
CLAD ≥ 2	4 (8.5)
FEV1 below 80% predicted pre-COVID	28 (59.6)
Ongoing treatment before COVID-19, n (%)	
Double regimen	3 (6.4)
Triple regimen	32 (68.1)
Quadruple regimen	12 (25.5)
Tacrolimus	24 (51.1)
Cyclosporine A	23 (48.9)
mTOR inhibitors	14 (29.7)
Antimetabolites	43 (91.4)
Low-dose steroids	46 (97.8)
Azithromycin prophylaxis	11 (23.4)
Disease severity, n (%)	
Asymptomatic	1 (2.1)
Mild	22 (46.8)
Moderate	7 (14.8)
Severe	13 (27.6)
Critical	4 (8.5)
NEWS2 score on assessment, n (%)	
0–2	26 (55.3)
3–5	7 (14.8)
≥ 6	12 (25.5)
ND	2 (4.3)
Initial radiology performed, n (%)	
CT	17 (35.0)
CXR	4 (8.5)

Table 2. Continued.

	All patients (n = 47)
Radiological findings n (%)	
CT – classic/probable COVID-19	15/17 (88.2)
CXR – classic/probable COVID-19	2/4 (50.0)
COVID-19 vaccine before disease, n (%)	9 (19.1)
Level of care, n (%)	
Outpatient	18 (38.1)
Hospitalized	29 (62.2)
COVID-19 management, n (%)	
Antimetabolite reduction/withdrawal	21 (44.7)
CNI reduction/withdrawal	0 (0)
mTOR inhibitors reduction/withdrawal	1 (2.1)
Prednisone increase	22 (46.7)
Betamethasone	10 (21.3)
Dexamethasone	9 (19.1)
Remdesivir	13 (27.6)
Respiratory support	22 (46.8)
Nasal Cannula	11 (23.4)
HFNC/NIV	7 (14.8)
Mechanical ventilation	4 (8.5)
LMWH /NOAC	27 (57.4)
Intensive care admission	8 (17.0)
Infectious complications	
Bacterial infections	15 (31.9)
Fungal infections	3 (6.4)
Length of stay, days, median (range)	
Hospital, n = 29	3 (1–48)
ICU, n = 8	7 (1–36)
Outcome, n (%)	
Dead during first admission	4/29 (13.8)
Dead within 28 days from diagnosis	2 (4.2)
Dead at the end of follow-up	7 (14.8)

BMI, body mass index; CCI, Charlson's comorbidity index; CKD, chronic kidney disease; CLAD, chronic lung allograft dysfunction; CNI, calcineurin inhibitors; COVID-19, coronavirus disease 2019; CT, computerized tomography; CXR, chest x-ray; HFNC/NIV, high flow nasal cannula/noninvasive ventilation; ICU, intensive care unit; IQR, interquartile range; mTOR, mechanistic target of rapamycin; LMWH, low molecular weight heparin; ND, not done; NEWS2, National Early Warning Score 2; NOAC, nonvitamin K antagonist oral anti-coagulants.

The immunosuppression protocol was temporarily altered for 34 (72%) patients. The most common changes were antimetabolite reduction/withdrawal in 20 (42.5%) cases and prednisone increase to at least 0.3mg/kg in 20 (42.5%). Twenty-seven patients (57%) received low molecular weight heparin or novel oral anticoagulants, nine (19.1%) received dexamethasone, 10 (21.3%) received betamethasone, and eight patients (17%) received no treatment at all. None of the patients

was treated with hydroxychloroquine (HCQ). 13 (27.6) received remdesivir (RDV).

The patients receiving RDV presented with moderate (two patients), severe (eight patients) or critical (three patients) disease and a median age of 62 (55–78) and a baseline eGFR 60.3 (6–93.3) ml/min/1.73 m². Patients receiving RDV were significantly older than those not receiving RDV ($P < 0.05$), whereas baseline kidney function was similar. There was no significant difference in eGFR pre- or postadmission for patients with vs without receiving RDV treatment ($P = 0.466$). All patients were treated with sulphamethoxazole/trimethoprim prophylaxis, and 11 (23.4%) were treated with azithromycin before COVID-19 infection. Fifteen (31.9%) patients developed a bacterial co-infection, three patients developed a fungal co-infection, but there were no recorded thromboembolic events. The treatment for bacterial and fungal infections was initiated at the discretion of the treating physician.

Outcome

Survival

The patients were followed for a median of 194 (23–509) days. Overall, seven LTx recipients (14.9%) died during the study period. Two patients (4.3%) died within 28 days of testing positive. The shortest time between PCR-positive diagnosis and death was 23 days. During the follow-up, another five patients died. Three out of the seven nonsurvivors died from causes directly related to COVID-19, two died because of malignancy, one patient died because of Mycobacterium abscessus infection, and one died because of an assumed association with rejection, more than 60 days after discharge. However, in the latter case, the autopsy also showed widespread diffuse alveolar damage and acute fibrinous and organizing pneumonia in the lungs but could not indicate a clear cause of death. Statistical analysis of overall survival between patients presenting with mild vs moderate or worse symptoms did not reach significance [$P = 0.053$] (Fig. 1).

Eight patients required admission to the intensive care unit (ICU) during their hospital stay; two of these died within 28 days from diagnosis/admission, whereas another three patients expired after more than four weeks, resulting in an ICU mortality of 62.5%.

Four out of thirteen patients (31%) receiving RDV died: three had critical, and one had severe disease. Granular data for all patients are presented in the supplementary table S1.

Table 3. COVID-19 symptoms, mild vs moderate or worse.

	Asymptomatic or mild (n = 23)	Moderate or worse (n = 24)	P-value
Males, n (%)	11 (47.8)	14 (58.3)	0.564
Age in years, median (range)	51 (10–73)	61 (51–78)	0.006*
Months since transplant, median (range)	54 (3–246)	58 (1–245)	0.9
First year after transplant, n (%)	3 (13.04)	5 (20.8)	0.7
Body mass index kg/m ² , median (range)	22.8 (14.0–33.0)	27.8 (22.0–39.9)	0.003*
Baseline eGFR ml/min/1.73m ² , median (range)	68.7 (29.4–185.3)	49.6 (6–93.3)	0.01*
Transplant type, n (%)			
Single lung	0	5 (20.8)	0.049*
Double lung	22 (96)	19 (79.2)	0.189
Heart–lung	1 (4)	0	0.489
Re-Transplantation, n (%)	0	4	0.109
Comorbidities, n (%)			
Hypertension	7 (30.4)	12 (50)	0.238
Diabetes	6 (26.1)	8 (33.3)	0.752
Cardiovascular	1 (4.4)	5 (20.8)	0.188
Malignancy	0 (0)	4 (17.4)	0.109
Obesity (BMI ≥ 30kg/m ²)	2 (8.7)	6 (25)	0.245
CKD stages 4–5	1 (4.4)	4 (17.4)	0.348
Ongoing treatment at COVID-19, n (%)			
Double regimen	2 (8.7)	1 (4.17)	0.601
Triple regimen	14 (60.9)	18 (75)	0.35
Quadruple regimen	7 (30.4)	5 (20.8)	0.517
Tacrolimus	16 (69.6)	8 (33.3)	0.02*
Cyclosporine A	7 (30.4)	16 (69.6)	0.02*
mTOR inhibitors	7 (30.4)	7 (29.2)	> 0.999
Antimetabolites	21(91.3)	20 (83.33)	0.667
Low-dose steroids	22 (95.7)	23 (95.8)	> 0.999
Azithromycin treatment	7 (30.4)	4 (16.7)	0.32
COVID-19 vaccine before infection	3 (13)	6 (25)	0.461
Lung function before COVID, n (%)			
CLAD	6 (28.6)	10 (43.5)	0.36
CLAD grade 2 or higher	2 (8.7)	2 (8.3)	> 0.999
FEV1 below 80% predicted pre-COVID	9 (39.1)	19 (79.2)	0.001*
FEV1% expected pre-COVID, median (range)	79 (36–106)	57 (21–100)	0.004*
Infectious complications, n (%)			
Bacterial infection	1	14	<0.0001*
Fungal infection	0	3	0.234
Outcome, n (%)			
28-day survival	23 (100)	22 (91.7)	0.489
All-time survival	22 (95.7)	18 (75.0)	0.097

BMI – body mass index, CKD – chronic kidney disease, CLAD – chronic lung allograft dysfunction, eGFR – estimated glomerular filtration rate, FEV1 – forced expiratory volume 1 second, mTOR – mechanistic target of rapamycin.

*Statistically significant.

Factors possibly associated with overall mortality

Univariate Cox analysis rendered a statistically significant result for preexisting malignancy [$P = 0.008$ (hazard ratio 7.68(1.71–34.56))], re-transplantation (Re-Tx) [$P = 0.02$ (7.28(1.38–38.48))] and bacterial co-infection [$P = 0.015$ (13.74(1.65–114.23))] (Table 4). Given the low number of events, no multivariate analysis was performed.

Functional/pulmonary outcome

All patients had pre-COVID spirometry data available. Twenty patients (43%) had a sequential spirometry from within 30 days of testing positive, 30 (64%) patients had a sequential spirometry between 31 and 90 days, and 27 (57%) patients had a sequential spirometry between 91 and 280 days after COVID-19.

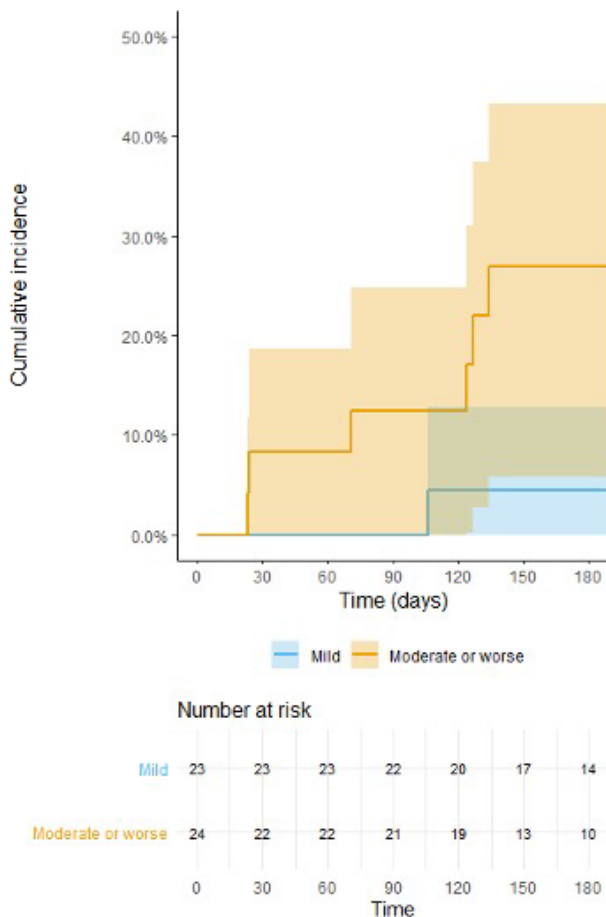


Figure 1 Cumulative incidence of mortality on disease severity. Incidence is presented with confidence intervals. Below the graph, patients at risk at corresponding time points, are presented.

There was a significant difference in Δ FEV1 between the patients presenting with asymptomatic or mild disease symptoms compared to patients with moderate or worse symptoms during the first two time periods ($P = 0.02$ and 0.03 , respectively). Still, this difference was not evident at later follow-up ($P = 0.17$) (Fig. 2). Three patients developed definite CLAD during the follow-up, one with mild and two with moderate or worse symptoms at presentation.

Radiology

Only 17 patients had an initial CT scan performed, which were all re-evaluated as previously described. Of these, four were moderate and 13 were severe or critical cases. There were no significant differences in the findings according to BTSI between the two groups. Details are presented in the supplementary table S2. Fifteen of the patients showed a “classic” or “probable” COVID pattern, and one patient showed an indeterminate

pattern. One patient presented a non-COVID pattern without ground-glass opacities but with pulmonary effusion. Both patients without classic or probable COVID patterns presented with severe symptoms. No signs of thromboembolism were detected.

COVID-19 and vaccination

Nine patients tested positive for SARS-CoV-2 after being vaccinated (Table 5). Only mRNA vaccines were used. Four had received two doses of Comirnaty® (Pfizer Europe, Brussels, Belgium), and three had received two doses of Spikevax® (Moderna, Cambridge, MA, USA). Two patients had only received one dose of Comirnaty®. The median time between the last dose and infection was 16 days (5–43), but no patient was tested for COVID-antibody titres a priori to infection. All patients survived until the end of follow-up, and only one patient was admitted to the ICU. The outcomes were not statistically significant when comparing to the unvaccinated cohort.

Analysis of the impact of first vs later waves of COVID-19 was also performed and is described in the supplementary information (S2) but did not render any statistically significant results of importance.

Discussion

The current study reports a national cohort of LTx recipients presenting the entire spectrum of COVID-19 severity and having the longest post-COVID follow-up yet available in the lung transplant literature. The analysis shows a 28-day, and overall mortality following COVID-19 in this unselected LTx population of 4.2% and 14.8%, respectively. The 28-day mortality is lower than in previously published LTx cohorts (9–34%) [6–10].

Early reports in the spring of 2020 indicated mortality rates exceeding 20% in solid organ transplant recipients (SOTR) getting infected with SARS-CoV-2 [4,16–18]. The dismal results were likely because of a combination of factors, including a bias towards hospitalized, more severe cases, limited knowledge about COVID-19 management, and underdiagnosing and underreporting of milder disease forms. Whereas the inclusion of outpatients with mild severity likely dilutes the mortality in the current study, the 28-day mortality in admitted patients (6.9%) still remains lower than previous reports. At the same time, the overall 30-day mortality among SOTRs in Sweden was found slightly higher (9.6%) [5], which contrasts with a recent US study where mortality was higher among LTx recipients [10].

Table 4. Survival analysis, univariate Cox model.

Comparison	Hazard ratio	95% CI	P-value
Male sex	1.40	0.31–6.26	0.661
Single lung transplant	1.49	0.18–12.42	0.711
Age, per decade	1.37	0.74–2.56	0.391
Re-transplant	7.28	1.38–38.48	0.020*
Transplanted less than a year before COVID infection	3.67	0.82–16.45	0.089
Vaccinated before COVID infection	++	++	++
Comorbidities			
Hypertension	0.57	0.11–2.95	0.503
Diabetes	2.57	0.31–21.37	0.382
Cardiovascular	1.32	0.16–11.01	0.795
Malignancy	7.68	1.71–34.56	0.008*
Obesity (BMI \geq 30kg/m ²)	1.01	0.12–8.54	0.980
CKD stages 4–5	1.37	0.16–11.35	0.773
Pulmonary function			
CLAD	1.94	0.39–9.62	0.416
CLAD \geq 2	2.78	0.32–24.32	0.355
FEV1 below 80%	++	++	++
Ongoing treatment before COVID-19			
Double regimen	2.71	0.32–22.67	0.358
Quadruple regimen	1.25	0.24–6.43	0.792
Tacrolimus	0.39	0.08–2.03	0.265
Cyclosporine A	2.54	0.49–13.12	0.265
mTOR inhibitors	0.97	0.19–4.98	0.968
Antimetabolites	0.92	0.11–7.64	0.938
Low-dose prednisone	++	++	++
Azithromycin prophylaxis	0.52	0.06–4.35	0.549
Clinical course			
Moderate or worse severity	6.20	0.75–51.51	0.091
Bacterial co-infection	13.74	1.65–114.23	0.015*
Fungal co-infection	2.82	0.34–23.49	0.338

CKD, chronic kidney disease; CLAD, chronic lung allograft dysfunction; FEV1, forced expiratory volume in 1 second; mTOR, mechanistic target of rapamycin.

* – Statistically significant, ++ – analysis yielded degenerate estimates and was removed.

Besides the inclusion of outpatients, other factors such as a dedicated COVID-hotline for transplant consultations established at our quaternary care centre early during the pandemic, the complete avoidance of HCQ, the restricted use of CNI reduction and a preference for early use of high flow nasal cannula to avoid mechanical ventilation whenever possible may have affected the outcome positively. Additionally, systemic corticosteroids were used liberally and early even for patients presenting with mild disease, although at a much lower dose for this subgroup, even before the RECOVERY trial presented evidence for dexamethasone in patients with respiratory support [19].

Potential baseline risk factors for poorer overall survival in univariate cox analyses were Re-Tx, preexisting cancer and bacterial co-infection. Cancer as a risk factor for death is not surprising, and bacterial infections also

intuitively add to the accumulated risk for death. Re-Tx is associated with a longer exposure to CNIs, which might present as lower renal function and a higher degree of cardiovascular complications. Re-Tx is also more commonly performed as a single LTx, which is associated with a lower PFT. A suboptimal pulmonary function has been associated with worse outcomes for both COVID-19 [20] in general and after lung transplantation [21]. Thus, one could hypothesize that low PFT pre-COVID-19 would be a risk factor for death. However, given the low number of events, multivariate analyses would not yield reliable results concerning the size of the effects or what factors are associated with death.

Higher age and BMI and a lower eGFR have been repeatedly identified as risk factors for more severe COVID-19 [5,22]. In contrast, evidence for a lower pre-

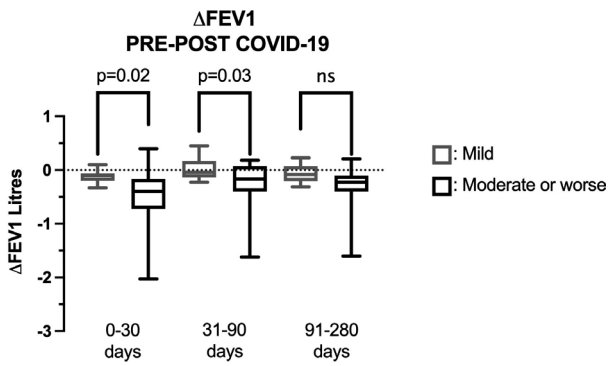


Figure 2 ΔFEV1 PRE-POST COVID-19. Spirometric difference between last spirometry before COVID and follow-up spirometries for mild vs moderate or worse symptomatology. Number of spirometries in each group are for 0–30: 12/8, for 31–90: 16/14 and for 91–280: 12/15.

COVID-19 PFT as a risk factor for disease severity is less extensive. The use of cyclosporine A (CyA) was more common in patients with more severe symptoms in our study. Thus, our results could not confirm the previously presented hypothesis of CyA curbing the COVID-19 development [23]. Interestingly, a large multicentre study in liver transplant recipients with COVID-19 reported a positive independent effect of tacrolimus on survival [24]. Whether this reflects different effects of one calcineurin inhibitor compared with the other or different effects related to the type of organ transplant needs to be addressed in larger and adequately matched analyses. Although there was no significant difference in overall survival between the mild and worse severity at presentation, it must be emphasized that the only death among mild severity patients was not in immediate proximity to the COVID-19 infection and was also associated with a Mycobacterium abscessus infection. Although mild disease at the time of COVID-PCR positivity was not associated with any risk of worsening and outpatient management appears feasible, it should be used with caution while maintaining frequent telemedicine contact.

The cause of the initial more pronounced loss of lung function in patients with more severe COVID-19 cannot be clearly identified. It could be caused directly by the sequelae of COVID-19 or increased immunologic activity in the graft, as antimetabolites were often reduced in more severe cases. On the contrary, COVID-19 literature has reported very few cases of rejection despite a significant reduction in immunosuppression, possibly because of the virus-induced immunosuppression and the lymphopenia seen in COVID-19 patients [5,25,26]. There are few studies with available pre-COVID-19

Table 5. Patients with COVID-19 after vaccination against COVID-19.

ID	Sex	Age	Transplant type	Months since transplant	CCI	BMI	eGFR	Immunosuppression	Vaccine	Doses given	Last dose to PCR positive (days)	Severity	Highest level of care	Alive at EoS
1	F	48	DL	30	1	23,7	36,9	Tac/Pred	Comirnaty®	2	13	Mild	Outpatient	1
2	M	61	DL	106	5	33,9	62,1	CyA/MMF/Pred	Spikevax®	2	22	Severe	Ward	1
3	M	59	DL	26	1	35,4	47,5	Tac/MMF/Pred	Spikevax®	2	23	Severe	Ward	1
4	M	69	DL	177	2	27,1	51,3	Tac/MMF/Pred/Eve	Spikevax®	2	48	Mild	Outpatient	1
5	F	51	DL	175	1	23	40,5	Tac/MMF/Pred	Comirnaty®	2	14	Mod.	Ward	1
6	M	64	SL	167	6	23	6,0	CyA/Pred/Eve	Comirnaty®	2	36	Mod.	Ward	1
7	F	61	DL	8	2	27	93,3	CyA/MMF/Pred	Comirnaty®	2	5	Severe	Ward	1
8	M	62	DL	92	5	28	10,0	CyA/Pred/Eve	Comirnaty®	1	16	Mod.	ICU	1
9	M	30	DL	14	0	22	93,3	Tac/MMF/Pred	Comirnaty®	1	8	Mild	Outpatient	1

BMI, body mass index; CCI, Charlson's comorbidity index; CyA, cyclosporine A; DL, double lung; eGFR, estimated glomerular filtration rate; EoS, end of study; Eve, everolimus; F, female; ICU, intensive care unit; M, male; MMF, mycophenolate mofetil; Mod., moderate; PCR, polymerase Chain reaction; Pred, prednisone; SL, single lung; Tac, tacrolimus.

FEV1 from healthy patients to explore the course of FEV1 dynamic post-COVID-19 in nontransplanted patients, and there is only limited evidence that worse symptoms are associated with lower post-COVID-19-FEV1 in a nontransplanted population [27]. Interestingly, a recent study found no significant difference in the loss of lung function between LTx recipients with COVID-19 patients and matched controls over 90 days [9]. However, no detailed information on disease severity at presentation was included in this study.

It is admittedly hard to present reliable retrospective post-COVID spirometry data. To circumvent some of the pitfalls, we use longitudinal comparisons of FEV1 only. The patients with milder symptoms initially provide more spirometries but eventually abstain from their follow-up examinations because of stable home spirometry. Furthermore, patients with a rapidly declining FEV1 have been brought from the follow-up site to the respective transplant centre, and unless they had performed their pre-COVID spirometry at the transplant centre, no more longitudinal data were available. Thus, rapidly declining patients predominantly in the moderate group and very stable patients predominantly in the mild group have fewer spirometries. Coronaviridae have previously been associated with a higher risk of CLAD [28]; however, with limited follow-up time regarding CLAD development, no conclusions can be drawn from the cases of CLAD post-COVID in the current study.

Increasing evidence indicates a weak response to SARS-CoV-2 vaccination in transplant recipients and COVID-19 following complete vaccination in SOTR [29–32]. Patients developing COVID-19 after vaccination in the current study tested positive at a median of 16 days after vaccination. Consequently, this could be an effect of early exposure to SARS-CoV-2 postvaccination for some patients rather than a limited effect of the anti-SARS-CoV-2 vaccination. Nonetheless, this implies that vaccinated transplant recipients will remain at risk for getting infected with SARS-CoV-2, and clinical evaluation of vaccination response with antibody levels or cellular immunity may be warranted. The possible interpretations of vaccinated LTx patients with COVID are limited because of an absence of statistically significant differences from the nonvaccinated cohort.

This study has several strengths as it has national coverage, including all LTx recipients in Sweden and identified essentially all those developing clinically manifest disease. In addition, virtually all lung transplanted patients in Sweden who needed hospital care during the first year of the pandemic were included herein, minimizing the risk of underestimating mortality in this

patient group. Furthermore, the median follow-up of 194 days is the longest reported in this setting so far.

Apart from a retrospective study's typical limitations, this report summarizes an evolutionary experience with changing guidelines and patients having different follow-up intervals. The regional autonomy and the varying experience of attending doctors in strained emergency wards have been expressed as the underlying reason for medical discrepancies such as oxygen being administered on varying indications. The nationally reported rationale for the low number of radiological examinations was to limit the COVID exposure within the respective hospitals. One possible consequence might be an underestimation of moderate cases according to NIH, in the cohort. However, the lack of worsening cases among the mild cases decreases the likelihood of this being a significant problem. This in combination with the lack of mandatory contact with the transplant centres for SOTR outpatients and the possibility that some patients with mild or asymptomatic disease did not contact health care implies that the study might still have overestimated the true mortality in this cohort. Nonetheless, COVID-19 prevalence in the Swedish LTx population was similar to the COVID-19 prevalence in Sweden as of 30 April (978 866 confirmed COVID-19 cases corresponding to 9.5%) [33], suggesting a near-complete identification of the COVID-19 cases. However, given the size of the cohort and the retrospective design that precludes any definite conclusions, we suggest the data should only be used for the generation of hypotheses.

Conclusion

The 28-day mortality found in the current study among Swedish LTx recipients with COVID is lower than previously reported. The results confirm that higher age, higher BMI, lower pre-COVID renal function and impaired lung function are associated with a more severe disease course for COVID-19 in LTx recipients. Furthermore, the results suggest an initial worsened pulmonary function for patients with more severe disease.

Authorship

JM: has participated in study design, data collection, statistical analysis, data interpretation, study performance and manuscript drafting. HL: has collected data and participated in data interpretation and writing of the manuscript. AA: has participated in data collection, radiological analysis and data interpretation. JE: has

participated in statistical analysis and data interpretation. KK: has participated in data interpretation and writing of the manuscript. AS: has participated in data interpretation and writing of the manuscript. VF: has participated in data interpretation and writing of the manuscript. MF: has participated in data interpretation and writing of the manuscript. JS: has participated in study design, study performance, data interpretation and writing of the manuscript. GD: has participated in data interpretation and writing of the manuscript. MO: has participated in study design, statistical analysis, study performance, data interpretation and manuscript drafting.

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Conflict of interest

JM has participated in advisory boards for Boehringer Ingelheim and GSK.

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with insights on airway management for COVID patients in their respective hospitals.

Data availability statement

Data for all patients were available on request with no patient lost to follow-up, and no patient was excluded because of missing data. Radiology was possible for all inpatients but not performed in eight cases, at the discretion of the attending physicians. Nine patients did not undergo same-site sequential post-transplant spirometries. According to NIH criteria, three of these patients presented as critical, four as severe and two as moderate. Poor performance status was the reason behind the missing spirometries for eight of the patients. For one of the patients, the reason was persistent Bell's palsy. Data is available from the corresponding author on reasonable request.

SUPPORTING INFORMATION

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

Appendix S1 Immunosuppression and prophylaxis protocol.

Appendix S2 COVID waves.

Table S1 Patient demographics, management and outcome in 47 lung recipients with COVID-Table 19 presented in chronological order.

Table S2 CT findings according to BSTI.

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