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One Year Into the Pandemic: Evolving COVID-19 Outcomes in Lung Transplant Recipients, a Single-center Experience

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Background. In the early months of the coronavirus disease 2019 (COVID-19) pandemic, our center reported a mortality rate of 34% in a cohort of 32 lung transplant recipients with COVID-19 between March and May 2020. Since then, there has been evolving knowledge in prevention and treatments of COVID-19. To evaluate the impact of these changes, we describe the clinical presentation, management, and outcomes of a more recent cohort of lung transplant recipients during the second surge and provide a comparison with our first cohort. **Methods.** We conducted a retrospective cohort study that included all consecutive lung transplant recipients who tested positive for severe acute respiratory syndrome coronavirus 2 between November 2020 and February 28, 2021. We compared baseline demographics and major outcomes between the first- and second-surge cohorts. **Results.** We identified 47 lung transplant recipients (median age, 60; 51% female) who tested positive for severe acute respiratory syndrome coronavirus 2 between November 2020 and February 28, 2021. The current cohort had a higher proportion of patients with mild disease (34% versus 16%) and fewer patients with a history of obesity (4% versus 25%). Sixty-six percent (n = 31) required hospitalization and were treated with remdesivir (90%) and dexamethasone (84%). Among those hospitalized, 77% (n = 24) required supplemental oxygen, and 22% (n = 7) required invasive mechanical ventilation. The overall 90-d mortality decreased from 34% to 17% from the first cohort to the second (adjusted odds ratio, 0.26; 95% confidence interval, 0.08-0.85; $P = 0.026$). **Conclusions.** Although COVID-19–associated mortality rate in lung transplant recipients at our center has decreased over time, COVID-19 continues to be associated with significant morbidity and mortality.

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INTRODUCTION

As of December 11, 2021, there have been over 49 million confirmed cases of coronavirus disease 2019 (COVID-19) in the United States, with almost 800 000 deaths.[1] Immunosuppressed state, particularly among solid organ transplant recipients, has emerged as a risk factor for severe disease and poor outcomes.[2] Existing literature on COVID-19 among solid organ transplant recipients reports mortality rates between 0% and 39%,[3-21] and more specifically between 8% and 39% among lung transplant recipients.[4,13-15,18,21]

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Our center reported on the findings and outcomes of the first 32 consecutive lung transplant recipients with COVID-19 identified between March 19, 2020, and May 29, 2020.[4] This early surge in cases was immediately followed by a brief period of no new cases between July and October of 2020. Coinciding with the larger national surge in the fall of 2020, our center once again began to identify new cases among lung transplant recipients in November of 2020.

Reports in the United States at both population and healthcare systems levels have found lower COVID-19–associated mortality over time since the early surge in the spring of 2020.[1,22,23] Although it remains uncertain if COVID-19 survival outcomes truly improved over time, there have been objective changes since the early surge, including increase in testing availability, new pharmacological treatments, shifting hospitalized demographics, growing experience, and improved availability of healthcare resources.[23-31] Follow-up reports are needed on COVID-19 outcomes among lung transplant recipients who incorporated these changes.

To characterize the trends in COVID-19 outcomes over time at our center, we performed a retrospective analysis describing the disease characteristics, management, complications, and outcomes of a more recent cohort of lung transplant recipients with COVID-19 at our center from November 2020 to February 2021 ("second surge") and provide a comparison with the first cohort from March and May of 2020 ("first surge").

MATERIALS AND METHODS

Subjects

This is a retrospective cohort study of all consecutive lung transplant patients followed by our center who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by polymerase chain reaction (PCR) testing between November 1, 2020, and February 28, 2021. Remarkably, there were no new laboratory-confirmed cases of acute infection in our lung transplant recipients between July and October 2020. We followed the same classification that was used in our first case series to facilitate direct comparison between the cohorts. Patients were classified as having mild COVID-19 if they did not require hospitalization; moderate COVID-19 if they required hospitalization; and severe COVID-19 if they were admitted to an intensive care unit or stepdown unit or required nonrebreather mask, high-flow nasal cannula, noninvasive ventilation, or invasive mechanical ventilation at any point during the disease course. Patients who had received at least 1 dose of a COVID-19 vaccine before their positive SARS-CoV-2 test were also included in the study.

Patient demographics, medical history, and baseline medications were obtained from the electronic health record (EHR). The definitions and criteria for baseline comorbidities are included in **SDC 1** (**SDC**, http://links.lww.com/TXD/A404).

Study Design

Throughout the study period, patients who contacted our program to report symptoms that were concerning for COVID-19 or exposure to a confirmed or suspected case of COVID-19 were advised to undergo SARS-CoV-2 testing. Additionally, patients received mandatory SARS-CoV-2 PCR testing on admission to the hospital and within 5 d before scheduled procedures, including pulmonary function tests and bronchoscopies.

Symptoms and vital signs at the time of SARS-CoV-2 testing and at the time of admission to hospital were obtained from the EHR (**SDC 2, SDC,** http://links.lww.com/TXD/A404).

The patients' clinical course, treatments, and laboratory values were obtained from the EHR, records provided by the managing teams at outside hospitals, and patients or their family members (**SDC 2, SDC,** http://links.lww.com/TXD/A404). We also compared baseline characteristics and outcomes between the first-surge and current cohorts. Our study treatment protocol was in accordance with COVID-19 clinical guidelines of our center and included treatment with monoclonal antibodies, dexamethasone, remdesivir, tocilizumab, and additional steroid therapy in conjunction with transplant infectious disease consult service (**SDC 3, SDC,** http://links.lww.com/TXD/A404).

Patients were followed until death or study end (May 31, 2021) to allow 3 mo of follow-up. This study was approved by the Columbia University Human Research Protection Office and the Institutional Review Board. The authors complied with the ethical standards and the US regulations.

Statistical Analysis

Statistical analysis was performed using Stata/SE version 15.1. Continuous and categorical variables were compared using the *t* test and 1-way analysis of variance. Survival in each cohort was compared using logistic regression and adjusted for relevant covariates, including age, obesity, bronchiolitis obliterans syndrome (BOS) status, single versus double lung transplant status, and preceding augmented immunosuppressive therapy.

RESULTS

Baseline Characteristics

We identified 47 consecutive lung transplant patients who tested positive for SARS-CoV-2 between November 1, 2020, and February 28, 2021. The median age was 65 y (range, 20–79 y). Patients were 51% female and 68% Caucasian. They had received a single lung transplant (60%) most commonly for interstitial lung disease (60%). The median time from transplant to COVID-19 diagnosis was 4.3 y (range, 20 d–18 y). Thirty percent of patients had BOS stage 1 or greater. The majority (81%) were on triple immunosuppression therapy with a cell-cycle inhibitor, calcineurin inhibitor, and prednisone. Nine patients (18%) were off cell-cycle inhibitors. Less than half (45%) of patients were taking azithromycin for BOS. Within the 3 mo before COVID-19 diagnosis, 34% of patients received immunosuppression augmentation, including 4 patients who received induction therapy for transplantation. Most patients had comorbidities at baseline: hypertension (75%), chronic kidney disease (62%), and diabetes (55%). Only 2 patients (4%) had obesity, though 38% were overweight. Six patients (13%) had Aspergillus infection within the past year. Three patients (6%) had received 1 dose, and 1 patient (2%) had received 2 doses of COVID-19 vaccine before their COVID-19 diagnosis, though none were fully vaccinated as defined by the Centers for Disease Control and Prevention. All 4 had been vaccinated after lung transplantation.

Baseline characteristics of patients with mild, moderate, and severe COVID-19 are reported in Table 1. The demographics were similar between the 3 severity groups, although

TABLE 1.

Baseline characteristics by COVID-19 severity

	Mild (n = 16)	Moderate (n = 18)	Severe (n = 13)	*P*
Age, median (IQR)	60 (48–69)	66 (57–72)	67 (60–73)	0.27
Sex, n (%)				0.15
Male	8 (50)	6 (33)	9 (69)	
Female	8 (50)	12 (67)	4 (31)	
Ethnicity, n (%)				0.24
Caucasian	13 (81)	10 (56)	9 (69)	
Hispanic	2 (13)	4 (22)	2 (15)	
African American	1 (6)	2 (11)	1 (8)	
Asian	0 (0)	2 (11)	1 (8)	
Transplant indication, n (%)				0.16
ILD	7 (44)	11 (61)	10 (77)	
COPD	4 (25)	3 (17)	2 (15)	
Sarcoid	0 (0)	2 (11)	1 (8)	
CF and non-CF bronchiectasis	5 (31)	1 (6)	0 (0)	
Other[a]	0 (0)	1 (6)	0 (0)	
Transplant type, n (%)				0.83
Single	8 (50)	10 (56)	8 (62)	
Double	8 (50)	8 (44)	5 (38)	
Years since transplant, median (IQR)	3.8 (2.9–8.9)	5.8 (2.5–10.4)	3 (1.2–8.6)	0.70
BOS stage, n (%)				0.36
1	0 (0)	4 (22)	1 (8)	
2	3 (19)	2 (11)	0 (0)	
3	2 (13)	1 (6)	1 (8)	
Baseline IS regimen, n (%)				
Mycophenolate <2000 mg/d	3 (19)	6 (33)	8 (62)	0.22
Mycophenolate ≥2000 mg/d	10 (63)	3 (17)	3 (23)	
Azathioprine <150 mg/d	1 (6)	3 (17)	0 (0)	
Azathioprine ≥150 mg/d	0 (0)	1 (6)	0 (0)	
No cell-cycle inhibitor[b]	2 (13)	5 (28)	2 (15)	
Tacrolimus	16 (100)	17 (94)[c]	13 (100)	1
Sirolimus	0 (0)	1 (6)[c]	0 (0)	
Cyclosporine	0 (0)	1 (6)	0 (0)	
Prednisone <10 mg/d	11 (69)	11 (61)	5 (38)	0.25
Prednisone ≥10 mg/d	5 (31)	7 (39)	8 (62)	
Azithromycin for BOS	7 (44)	8 (44)	6 (46)	0.99
Recent IS augmentation, n (%)	7 (44)[d]	4 (22)[e]	5 (38)[d,f]	0.40
Induction (basiliximab + solumedrol)	3 (19)	0 (0)	1 (8)	
Steroid pulse	1 (6)	1 (6)	3 (23)	
Steroid taper	2 (13)	1 (6)	0 (0)	
rATG	2 (13)	0 (0)	1 (8)	
Immune-modulating (ECP, IVIG)	0 (0)	3 (17)	1 (8)	
Received COVID-19 vaccine, n (%)	1 (6)	1 (6)	2 (15)	0.60
Only first dose	1 (6)	0 (0)	2(15)	
Both doses	0 (0)	1 (6)	0 (0)	
BMI, mean (IQR)	24.2 (21.7–27.6)	24.3 (22.4–26.4)	24.4 (24–25)	0.92
Comorbidities, n (%)				
Hypertension	10 (63)	14 (78)	11 (85)	0.38
CKD	6 (38)	14 (78)	9 (69)	0.056
Heart disease	3 (17)	4 (22)	5 (38)	0.46
Diabetes	9 (56)	7 (39)	10 (77)	0.11
Overweight (BMI 25–29.9)	5 (31)	6 (33)	7 (54)	0.41
Obesity (BMI ≥30)	1 (6)	1 (6)	0 (0)	0.40
Active malignancy	2 (13)	3 (17)	1 (8)	0.77
Recent Aspergillus infection	0 (0)	1 (6)	5 (38)	0.003

[a]Other transplant indication includes LAM.
[b]Patients were off cell-cycle inhibitors for active or history of malignancy, infection (Cryptococcus), treatment with alemtuzumab, or cytopenia.
[c]One patient was taking both tacrolimus and sirolimus.
[d]One patient received both thymoglobulin and steroid pulse.
[e]One patient received both a steroid pulse and ECP.
[f]One patient received both induction therapy and a steroid pulse.
BMI, body mass index; BOS, bronchiolitis obliterans syndrome; CF, cystic fibrosis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ECP, extracorporeal photopheresis; ILD, interstitial lung disease; IQR, interquartile range; IS, immunosuppression; IVIG, intravenous immunoglobulin; LAM, lymphangioleiomyomatosis; rATG, rabbit antithymocyte globulin.

patients with mild disease tended to be younger. Patients who had prior Aspergillus infection more commonly had severe disease.

Clinical Presentation

Thirty-four percent of patients had mild, 38% moderate, and 28% severe COVID-19. Median duration of symptoms before SARS-CoV-2 testing was 3 d (range, 0–14 d). Seven patients (15%) had a positive SARS-CoV-2 test on asymptomatic preprocedural testing. These patients tended to have mild disease, with 2 patients ultimately requiring hospitalization. Three patients (6%) tested positive for SARS-CoV-2 while already admitted for non–COVID-19 diagnoses and had presumed nosocomial COVID-19 infection.

Symptoms reported at time of diagnosis included fever (38%), cough (72%), dyspnea (70%), gastrointestinal symptoms (51%), and altered mental status (15%). Patients who had fever, cough, or dyspnea were more likely to develop moderate or severe disease. Abnormal vital signs among the 31 patients admitted for COVID-19 and those who tested positive for SARS-CoV-2 as inpatient included hypoxemia (55%), tachypnea (65%), and tachycardia (58%). Patients who presented with hypoxemia, tachypnea, or altered mental status were more likely to develop severe disease. Symptoms at the time of diagnosis for all patients and vital sign abnormalities for hospitalized patients are reported in Table 2.

Median values of laboratory results obtained upon admission for moderate and severe COVID-19 patients are shown in **Table S1** (**SDC,** http://links.lww.com/TXD/A404). Higher levels of C-reactive protein and lactate dehydrogenase upon admission were more common in those who developed severe disease.

Most hospitalized patients (68%) had new pulmonary infiltrates on admission, with the majority (57%) having bilateral infiltrates, regardless of transplant type (Table 3). Throughout their disease course, 92% of patients who required supplemental oxygen developed pulmonary infiltrates, and all patients with severe disease exhibited diffuse, bilateral infiltrates on imaging. Additional radiographic data, categorized by COVID-19 severity, are shown in Table 3.

Treatment

Thirty-one patients (66%) required hospitalization for moderate-to-severe COVID-19. Among those admitted, 77% required supplemental oxygen, including mechanical ventilation in 7 patients (23% of the hospitalized cohort). During their hospitalization for COVID-19, 26 patients (84%) were treated with dexamethasone, and 28 (90%) received remdesivir. Twenty-seven hospitalized patients (84%) received broad-spectrum antibiotics. Cell-cycle inhibitors were continued without dose reduction in most patients with mild disease. In contrast, cell-cycle inhibitors were either held or continued at a lower dose in 61% of patients hospitalized with moderate-to-severe disease. Steroid pulse and/or taper was also initiated in 15 patients who were hospitalized (48%). Four patients required renal replacement therapy.

Ten patients (21%) from the entire cohort received monoclonal antibody-based treatment at a median of 7 d within symptom onset. Six of these patients continued to be managed in the outpatient setting, and 2 developed severe COVID-19 (Table 4).

Clinical Outcomes

The overall 90-d all-cause mortality from our center's second COVID-19 cohort from November 2020 to February 28, 2021, was 17%. The mortality rate among patients with severe disease was 54%. There was no mortality among patients who did not develop hypoxemia.

Of the 31 patients who required hospitalization, 6 patients (19%), all with severe disease, died during their COVID-19 hospitalization. All 18 hospitalized patients with moderate disease were discharged home post–COVID-19 admission. Two patients, one with severe disease and another with moderate disease, both of whom required supplemental oxygen during admission, were discharged and subsequently died after their index COVID-19 admission.

Seven patients (15%) from the entire cohort required invasive mechanical ventilation with a median of 11 d on the ventilator; 5 of those patients ultimately died. Most of the patients with severe disease (86%) who survived their COVID-19 hospitalization remained alive at the end of the study period with 33% still requiring supplemental oxygen. Most of the patients (63%) with moderate disease who required supplemental oxygen during hospitalization were discharged on room air; only 3 patients with moderate disease remained on supplemental oxygen by the end of the study.

TABLE 2.

Clinical presentation as reported by outpatients and at hospital admission for inpatients by COVID-19 severity

	Mild (n = 16)	Moderate (n = 18)	Severe (n = 13)	*P*
Duration of symptoms (d) before testing, median (IQR)	2 (0–7)	3 (2–6)	3 (2–3)	0.72
Detected on routine testing, n (%)	5 (31)	1 (6)	1 (8)	0.078
Prior COVID-19 vaccination, n (%)[a]	1 (6)	1 (6)	2 (15)	0.60
Fever, n (%)	1 (6)	13 (72)	4 (31)	<0.001
Cough, n (%)	8 (50)	15 (83)	11 (85)	0.048
Dyspnea, n (%)	4 (25)	16 (89)	13 (100)	<0.001
GI symptoms, n (%)	6 (38)	12 (67)	6 (46)	0.23
Hypoxemia, n (%)	–	5 (28)	12 (92)	<0.001
Tachypnea, n (%)	–	8 (44)	12 (92)	0.0048
Tachycardia, n (%)	–	8 (44)	10 (77)	0.07
Hypotension, n (%)	–	1 (6)	3 (23)	0.16
Altered mental status, n (%)	–	1 (6)	6 (46)	0.018

[a]None of the patients with prior COVID-19 vaccination were fully vaccinated as defined by Centers for Disease Control and Prevention guidelines.
IQR, interquartile range; COVID-19, coronavirus disease 2019; GI, gastrointestinal.

TABLE 3.

Radiographic changes secondary to COVID-19 by severity

Radiographic features	Mild (n = 16)	Moderate (n = 18)	Severe (n = 13)	*P*
New infiltrates on admission, n (%)	–	12 (67)	9 (69)	0.89
Double lung transplant patients, n (%)		6 (33)	4 (31)	
Bilateral allograft infiltrates		2	4	
Single lung transplant patients, n (%)		6 (33)[a]	5 (38)	
Predominant native infiltrates		1	0	
Predominant allograft infiltrates		2	1	
Bilateral infiltrates		2	4	
New infiltrates during disease course, n (%)	3 (19)[b]	13 (72)	13 (100)	<0.001
Double lung transplant patients, n (%)	2 (13)	6 (33)	5 (38)	
Bilateral allograft infiltrates	1	6	5	
Single lung transplant patients (%)	1 (6)	7 (39)[a]	8 (62)	
Predominant native infiltrates	0	1	0	
Predominant allograft infiltrates	1	2	0	
Bilateral infiltrates	0	3	8	
Focal infiltrates, n (%)	2 (13%)	1 (6%)	0 (0%)	0.41
Diffuse infiltrates, n (%)	1 (6%)	11 (61%)	13 (100%)	<0.001
No infiltrates, n (%)	13 (81%)	5 (28%)	0 (0%)	<0.001
Chest CT available, n (%)	9 (56%)	15 (83%)	6 (46%)	
GGO alone	3	5	3	0.77
Consolidation alone	0	2	0	0.37
Both	0	3	3	0.032
None	6	5	0	0.027

[a]Missing laterality information for 1 patient.
[b]For patients with mild disease, these data are from chest imaging obtained during follow-up.
COVID-19, coronavirus disease 2019; CT, computed tomography of the chest; GGO, ground glass opacities.

Complications including thromboembolism, transaminitis, neurological events, and coinfections were more common among patients with severe disease (Table 5). One-third of the severe disease cohort required renal replacement therapy. Median values of abnormal laboratory results during disease course are shown in **Table S1** (**SDC**, http://links.lww.com/TXD/A404). Patients with severe disease more commonly had elevated creatinine, aspartate aminotransferase, C-reactive protein, procalcitonin, lactate dehydrogenase, and troponin during hospitalization.

The average time to first negative SARS-CoV-2 PCR was 56 d in the 34 patients with available retesting data and did not differ greatly among severity groups (Table 6). One patient with severe disease who required readmission intermittently had positive SARS-CoV-2 test results at 115 d after the first positive test.

Comparison to First-Surge Cohort

Comparisons of the baseline demographics and major outcomes between the first- and second-surge cohorts are shown in Table 7.

Under crisis standards of care in the spring of 2020, where testing was severely limited, PCR testing at our center was almost exclusively performed on symptomatic patients, mostly in those presenting to the emergency department. Asymptomatic and preprocedural screening were not available at the time. As testing became more widely available over the course of the pandemic, the demographics of COVID-19 patients from the second surge at our center evolved to include higher proportion of patients with milder disease (16% versus 34%; $P = 0.70$) and lower proportion of severe disease (28% versus 41%; $P = 0.234$).[4] In fact, 15% of patients from the current cohort were asymptomatic at the time of positive preprocedure PCR testing. The current cohort also contained a lower percentage of hospitalized (66% versus 84%; $P = 0.07$) and mechanically ventilated (15% versus 31%; $P = 0.08$) patients.[4] The duration of reported symptoms before SARS-CoV-2 testing tended to be shorter in the current cohort (3 versus 4 d; $P = 0.11$).[4] One major difference in patient baseline characteristics between the 2 cohorts was the lower proportion of patients with obesity in the second-surge cohort (4% versus 25%; $P = 0.02$).[4] Another difference was the higher proportion of patients on tacrolimus at baseline in the current cohort (98%, versus 75%; $P = 0.004$). Otherwise, patient baseline characteristics were similar between the 2 groups.

Major differences in pharmacological treatments reflect standard of care from each time period. Most of the patients in the first-surge cohort received hydroxychloroquine (84%) and azithromycin (75%), whereas none of the patients from the current cohort received either of these treatments. Additionally, whereas less than half of patients in the first-surge cohort (44%) received steroid augmentation, 84% of the current cohort with hypoxemia received corticosteroids equivalent in dose of dexamethasone 6 mg/d or higher per updated treatment guidelines. There was a trend toward reduced mortality in the second-surge cohort in both unadjusted and adjusted analyses (17% versus 34%; adjusted odds ratio, 0.26; 95% confidence interval, 0.08-0.85; $P = 0.026$; Figure 1A). This trend toward reduced mortality in the second-surge cohort was also observed in both the unadjusted and adjusted analyses of patients with

TABLE 4.

Treatments administered in patients with COVID-19 by severity

	Mild (n = 16)	Moderate (n = 18)	Severe (n = 13)	*P*
Highest oxygen requirement, n (%)	–			<0.001
MV		0 (0)	7 (54)	
HFNC		0 (0)	4 (31)	
NIV		0 (0)	0 (0)	
NRB		0 (0)	2 (15)	
NC		11 (61)	0 (0)	
Dexamethasone, n (%)	–	13 (72)	13 (100)	0.039
Steroid augmentation beside dexamethasone, n (%)	–	5 (28)	10 (77)	0.006
Remdesivir, n (%)	–	15 (83)	13 (100)	0.13
<5 d[a]		3	2	
5 d		12	10	
10 d		0	1	
Convalescent plasma, n (%)	–	3 (17)	2 (15)	0.93
Tocilizumab, n (%)	–	0 (0)	2 (15)	0.09
mAb therapy (before admission), n (%)	6 (38)	2 (11)[b]	2 (15)	0.15
Bamlanivimab	6	1	2	–
Casirivimab/imdevimab	0	1	0	–
Days from positive test to mAb therapy, mean (range)	4.2 (1–10)	5.5 (5–6)	4.5 (4–5)	
Days from symptoms to mAb therapy, mean (range)	4.8 (2–7)	4.5 (2–7)	7 (7–7)	
Days from mAb therapy to admission, mean (range)	–	6 (1–11)	2 (0–4)	
Cell-cycle inhibitor reduced or held, n (%)[c]	1 (6%)	9 (50%)	10 (77%)	<0.001
Broad-spectrum antibiotics on admission, n (%)	–	14 (78%)	12 (92%)	0.26
Broad-spectrum antibiotics during disease course, n (%)	–	13 (72%)[d]	13 (100%)	0.039
Dialysis, n (%)	–	0 (0%)[e]	4 (31%)[e]	0.009
Vasopressors, n (%)	–	0 (0%)	7 (54%)	<0.001
Enrolled in clinical trial, n (%)	–	0 (0%)	4 (31%)	0.01

[a]Five patients received less than the standard 5-d course because of improvement of oxygenation status to room air or complications including concern for hepatotoxicity or acute kidney injury.
[b]One patient received mAb after their index COVID-19 admission and is not included in this total.
[c]One patient with mild disease, 5 patients who had moderate disease, and 2 patients who had severe disease were already off cell-cycle inhibitors at baseline and are not included in these totals.
[d]Antibiotic data could not be determined for 1 patient who was admitted to an outside hospital.
[e]One patient in both the moderate and severe groups was already on hemodialysis at baseline and not included in this total.
COVID-19, coronavirus disease 2019; HFNC, high flow nasal cannula; mAb, monoclonal antibody; MV, mechanical ventilation; NC, nasal cannula; NIV, noninvasive ventilation; NRB, nonrebreather.

moderate-to-severe COVID-19 (26% versus 41%; adjusted odds ratio, 0.28; 95% confidence interval, 0.79-1.03; $P = 0.056$; Figure 1B).

DISCUSSION

Notably, after the first surge in the spring of 2020 at our center, there were no new acute COVID-19 cases between July and October 2020. This initial brief pause in new cases among our center's lung transplant recipients coincided with local and national trends and may have reflected improved adherence to social distancing and self-isolation practices. We then identified 47 consecutive lung transplant recipients with positive SARS-CoV-2 between November 1, 2020, and February 28, 2021, and described their clinical presentations, management, and outcomes in this report. It is worthwhile noting that our study period preceded the rise of Delta strain (B.1.617.2), which is currently the predominant variant in the United States and is associated with higher rates of transmission and severe disease.[1]

In this second-surge cohort, we report an overall 90-d mortality rate of 17% in lung transplant recipients with COVID-19. As demonstrated in prior studies, severe COVID-19 with hypoxemia requiring supplemental oxygen, particularly among those requiring mechanical ventilation, was associated with increased mortality.[13,14,18] On the contrary, the subset of patients who did not develop hypoxemia had favorable outcomes with no mortality observed. As for the patients initially requiring low-level supplemental oxygen support, overall mortality was still quite low with no inpatient mortality and 1 patient who died after discharge. Our findings suggest that the development of hypoxemia requiring supplemental oxygenation is an important prognostic marker of poor outcomes in lung transplant recipients.

Our findings also suggest a trend toward improved mortality in the second-surge COVID-19 cohort at our center. We feel that it is imperative to provide an updated mortality outcome for this population from a more recent study period that incorporated current evidence-based treatments. Without the extraordinary healthcare system capacity constraints and limited testing availability experienced in the early months of the pandemic, the lower mortality rate in our current report likely represents a more accurate estimate of COVID-19–associated mortality in this population.

We acknowledge that there are many inherent differences in characteristics between 2 study cohorts of our center in this comparative analysis. The challenges uniquely present at the onset of the pandemic—including COVID-19 being a novel disease with limited prior knowledge and experience in additional to scarcity of healthcare resources inherently—resulted in the higher illness severity of the first-surge cohort.

TABLE 5.

Clinical course and complications in patients with moderate and severe COVID-19

	Moderate (n = 18)	Severe (n = 13)	*P*
Died, n (%)	1 (6)	7 (54)	<0.001
Required mechanical ventilation, n (%)	–	7 (54)	–
Days on ventilator	–	Median, 11 (IQR, 3–33) Mean, 22.9 (range, 3–74)	–
Received ECMO support, n (%)	0 (0)	0 (0)	–
Total LOS (d), median (IQR)	9 (5–15)	28 (10–57)	0.025
Combined ICU/SDU LOS (d)	–	Median, 13 (IQR, 10–36) Mean, 29 (range, 0–106)	–
Complications, n			
AKI	10 (63)[a]	11 (85)[a]	0.083
New arrhythmia	2 (13)	2 (15)	0.74
VTE/arterial thrombi	0 (0)	4 (31)	0.011
Transaminitis	6 (38)	10 (77)	0.023
Neurological events	1 (6)	7 (54)	0.006
Coinfection	5 (31)	9 (69)	0.031
Respiratory[b]	2 (13)	5 (38)	0.092
BSI[c]	2 (13)	2 (15)	0.78
CMV	1 (6)	3 (23)	0.18
Other[d]	2 (13)	3 (23)	0.43

[a]One patient was already on hemodialysis at baseline and is not included in this total.
[b]Respiratory infections included rhinovirus, enterovirus, *Aspergillus fumigatus, Pseudomonas aeruginosa*, *Stenotrophomonas, Klebsiella*, *E coli*, and methicillin-resistant *Staphylococcus aureus*.
[c]Blood stream infections included *Staphylococcus epidermidis*, vancomycin-resistant Enterococcus.
[d]Other coinfections included Epstein-Barr virus; gastrointestinal cultures positive for *Clostridium difficile*, Yersinia; and urine cultures positive for *Pseudomonas aeruginosa*, BK virus, and Citrobacter.
AKI, acute kidney injury; BSI, blood stream infection; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenator; *E coli*, *Escherichia coli*; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; SDU, step down unit; VTE, venous thromboembolism.

Over the course of the pandemic, COVID-19 demographics of our center evolved to include more patients with milder disease and fewer patients with severe disease. To attenuate the potential bias toward improved outcome from the higher number of mild COVID-19 patients in this cohort, we performed a logistic regression on only moderate-to-severe COVID-19 patients from both cohorts. The trend toward improved mortality in the second-surge cohort with higher severity of illness persisted. We suspect that earlier and improved access to healthcare resources and updated COVID-19 treatments may have contributed to improved mortality in this population.

To our knowledge, we provide the first report on prolonged SARS-CoV-2 viral shedding in lung transplant recipients. Similar findings were described in kidney transplant recipients with 1 study reporting a kidney transplant recipient with a persistently positive nasal SARS-CoV-2 PCR at >66 d from symptom onset despite clinical recovery,[32] and another reported 25% of its kidney transplant recipient cohort with persistently positive respiratory PCR at day 30 after symptom onset.[33] Whether prolonged respiratory viral shedding also signifies a prolonged viral transmission window in lung transplant recipients with COVID-19 remains unknown. Furthermore, the clinical correlation of a prolonged positive respiratory tract viral PCR to quantitative viral load, cycle threshold, and viral cell culture in this immunocompromised population remains to be studied.

Our study has many strengths and provides the largest single-center cohort on the impact of COVID-19 in lung transplant recipients beyond the early months of the pandemic. The therapeutic regimen and management practices used in our study incorporated the most current evidence-based guidelines. Given limited data to guide management of lung transplant recipients with COVID-19, our protocol represents relatively large experience of our center and was associated with reasonable outcomes compared with the general population and prior cohorts. Our report also contains the largest number of lung transplant recipients with COVID-19 who were effectively managed in an ambulatory setting.

This retrospective cohort study is limited by its small sample size. There may have been patients with mild symptoms who were not tested and those who tested positive but did not self-report to our center. There was also likely a lead-time bias when comparing outcomes between the 2 cohorts with earlier diagnosis (including through preprocedural testing) and earlier presentation after symptom onset in the second-surge cohort. Finally, long-term functional and survival outcomes are not yet available for reporting.

In summary, COVID-19 in lung transplant recipients is associated with lower but still significant mortality in the second surge of the pandemic. Further studies will be required to assess longer-term outcomes, including mortality, functional status, and graft function. Additionally, the impact of COVID-19 vaccination and the rise of Delta, Omicron, and other variants on disease frequency, severity, and mortality in lung transplant patients will have to be studied.

TABLE 6.

Clinical outcomes by COVID-19 severity

Outcomes	Mild (n = 16)	Moderate (n = 18)	Severe (n = 13)	*P*
Mortality, n (%)[a]	0 (0)[a]	1 (6)[a]	7 (54)[b]	<0.001
New O_2 requirement on discharge, n (%)	–	4 (22)	5 (38)	0.021
On O_2 at follow-up, n (%)	0 (0)	3 (17)	2 (15)	0.087
Discharged to home, n (%)	–	18 (100)	4 (31)	0.0018
Time until first negative swab (d), median (IQR)	46 (22–99) (n = 15)	53 (28–71) (n = 13)	46 (38–55.5) (n = 6)	0.66

[a]One patient was discharged home and died suddenly at home.
[b]One patient was readmitted from a subacute rehab facility 8 d after initial discharge for non–COVID-19 pneumonia (PCR testing negative) and CMV viremia.
CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; IQR, interquartile range; PCR, polymerase chain reaction.

TABLE 7.

Comparison between first and second cohorts

	First-surge cohort (n = 32)	Second-surge cohort (n = 47)	*P*
Age, y, median (IQR)	65 (51–69)	65 (57–72)	0.52
Sex, n (%)			
Female	16 (50)	24 (51)	0.93
Ethnicity, n (%)			0.45
Caucasian	16 (50)	32 (68)	
Hispanic	9 (28)	8 (17)	
African American	7 (22)	4 (8)	
Asian	0 (0)	3 (6)	
Transplant indication, n (%)			0.11
ILD	15 (47)	28 (59)	
Transplant type, n (%)			0.85
Single	17 (53)	26 (55)	
Years since transplant, median (IQR)	5.6 (2–8.6)	4.3 (2–9.7)	0.77
BOS stage, n (%)			0.40
1	4 (13)	5 (11)	
2	2 (6)	5 (11)	
3	1 (3)	4 (9)	
Baseline IS regimen, n (%)			
Mycophenolate ≥2000 mg/d	13 (41)	16 (34)	0.10
Azathioprine ≥150 mg/d	2 (6)	1 (2)	
No cell-cycle inhibitor	1 (3)	9 (19)	
Tacrolimus	24 (75)	46 (98)	0.004
Prednisone ≥10 mg/d	7 (22)	20 (43)	0.06
Azithromycin for BOS	17 (53)	21 (45)	0.47
Recent IS augmentation, n (%)	8 (25)[a]	16 (34)[b]	0.40
Comorbidities, n (%)			
Hypertension	18 (56)	35 (74)	0.09
CKD	21 (65)	29 (62)	0.82
Heart disease	6 (19)	12 (26)	0.49
Diabetes	14 (44)	26 (55)	0.32
Obesity (BMI ≥30)	8 (25)	2 (4)	0.018
Active malignancy	1 (3)	6 (13)	0.14
Duration of symptoms (d) before testing, median (IQR)	4 (1.75–7.25)	3 (1.75–6)	0.11
Disease severity, n (%)			
Mild disease	5 (16)	16 (34)	0.070
Moderate disease	14 (44)	18 (38)	0.633
Severe disease	13 (41)	13 (28)	0.234
Hospitalization, n (%)	27 (84)	31 (66)	0.074
Mechanical ventilation, n (%)	10 (31%)	7 (15)	0.084
Mortality, n (%)	11 (34)	8 (17)	0.078

[a]Three percent received induction therapy (basiliximab + solumedrol), 3% received steroid pulse, 25% received steroid taper, and 8% received rATG.
[b]Eight percent received induction therapy (basiliximab + solumedrol), 11% received steroid pulse, 6% received steroid taper, and 8% received rATG.
BMI, body mass index; BOS, bronchiolitis obliterans syndrome; CKD, chronic kidney disease; ILD, interstitial lung disease; IQR, interquartile range; IS, immunosuppression.

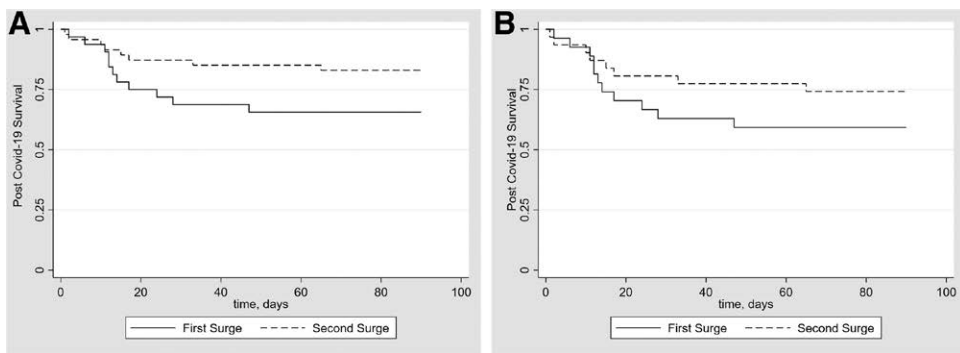

FIGURE 1. A, Kaplan-Meier Plot of the probability of survival from COVID-19 diagnosis to day 90 in lung transplant recipients with COVID-19 from the first and second surges. There was a trend toward reduced 90-d mortality in the second-surge cohort in both unadjusted and adjusted analyses (17% vs 34%; adjusted OR, 0.26; 95% CI, 0.08-0.85; $P = 0.026$). B, Kaplan-Meier Plot of the probability of survival from COVID-19 diagnosis to day 90 in lung transplant recipients with moderate-to-severe COVID-19 from the first and second surges. There was a trend toward reduced 90-d mortality in the second-surge cohort of patients with moderate-to-severe COVID-19 in unadjusted and adjusted analyses (26% vs 41%; adjusted OR, 0.28; 95% CI, 0.79-1.03; $P = 0.056$). CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio.

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