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COVID-19 in lung transplant recipients: A single center case series from New York City

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There are limited data describing COVID-19 in lung transplant recipients. We performed a single center, retrospective case series study of lung transplant patients followed by the Columbia Lung Transplant program who tested positive for SARS-CoV-2 between March 19 and May 19, 2020. Thirty-two lung transplant patients developed mild (16%), moderate (44%), or severe (41%) COVID-19. The median age of patients was 65 years, and the median time from lung transplant was 5.6 years. Symptoms included cough (66%), dyspnea (50%), fever (47%), and gastrointestinal upset (44%). Patients received hydroxychloroquine (84%), azithromycin (75%), augmented steroids (44%), tocilizumab (19%), and remdesivir (9%). Eleven patients (34%) died at a median time of 14 days from admission. Complications during admission included: acute kidney injury (63%), transaminitis (31%), shock (31%), acute respiratory distress syndrome (25%), neurological events (25%), arrhythmias (22%), and venous thromboembolism (9%). Compared to patients with moderate COVID-19, patients with severe COVID-19 had higher peak white blood cell counts (15.8 vs 7 × 10^3/uL, P = .019), C-reactive protein (198 vs. 107 mg/L, P = .010) and D-dimer (8.6 vs. 2.1 ug/mL, P = .004) levels, and lower nadir lymphocyte counts (0.09 vs. 0.4 × 10^3/uL, P = .006). COVID-19 is associated with severe illness and a high mortality rate in lung transplant recipients.

KEYWORDS
clinical research/practice, complication: infectious, infection and infectious agents - viral, lung failure/injury, lung transplantation/pulmonology, patient survival

1 | INTRODUCTION

In March 2020, New York City quickly became an epicenter of the worldwide coronavirus disease 2019 (COVID-19) pandemic. By June 8, 2020, there had been 204,253 confirmed cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, resulting in 52 920 hospital admissions and 17 169 deaths.[1] While data on the impact of COVID-19 on solid organ transplant recipients are beginning to emerge, it remains limited.[2-10] Lung transplant recipients who have contracted SARS-CoV-2 are a particularly informative patient population to study both in light of the predominantly respiratory manifestations of COVID-19[11] as well as the significant role that a dysregulated immune response plays in immunocompetent patients with severe disease.[12] The impact of COVID-19 on the lung allograft and the extent to which the immune dysregulation transpires in the setting of immunosuppression in this patient population remain entirely unknown.

Recently, our center described our earliest experience with SARS-CoV-2 in 90 solid organ transplant recipients, which included 17 of our lung transplant patients.[7] As the incidence of COVID-19 has continued to increase, our objective now is to add to that data and describe the baseline characteristics, clinical presentations, treatments, and early outcomes among our SARS-CoV-2-positive lung transplant patients, specifically.

2 | METHODS

2.1 | Subjects

All consecutive lung transplant patients followed by our center who tested positive for SARS-CoV-2 (by nasopharyngeal or oropharyngeal swab) between March 19, 2020 and May 19, 2020 were included in the study. Patients were excluded if there was no information available regarding their clinical course. Patients were categorized as having mild COVID-19 if they did not require hospitalization, moderate COVID-19 if they were admitted to a hospital ward, or severe COVID-19 if they were admitted to an ICU or required non-rebreather mask, high-flow nasal cannula, or invasive mechanical ventilation at any point during disease course. Patient demographics, prior medical history, pulmonary function tests (PFTs), and baseline medications were obtained from the electronic medical record. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 based on the average of the 3 most recent creatinine values prior to the onset of COVID-19. Baseline heart disease was defined as any history of obstructive coronary artery disease, or the presence of reduced left ventricular ejection fraction, diastolic dysfunction, or severe valvular disease on the most recent echocardiogram on file prior to the onset of COVID-19. Obesity was defined as body mass index (BMI) of greater than 30 kg/m^2 documented in the clinical record prior to the onset of COVID-19. Bronchiolitis obliterans syndrome (BOS) was graded 0-3 according to the ISHLT classification system.[13]

2.2 | Study design

Throughout the study period, patients who contacted our program to report symptoms that were consistent with COVID-19 or an exposure to a confirmed or suspected case of COVID-19 were advised to undergo SARS-CoV-2 testing. We did not perform routine SARS-CoV-2 testing for all patients in the absence of suspicious symptoms or exposure. We were notified of all positive SARS-CoV-2 tests by the patients or their family members, their managing physicians at outside hospitals, or the lung transplant physician at our center. The patients' symptoms and abnormal vital signs at the time of SARS-CoV-2 testing and at the time of admission to hospital (if differed) were obtained from the patient by phone or documentation from the medical clinic or emergency department visit, including presence of cough, dyspnea, gastrointestinal (GI) upset (vomiting or diarrhea), fever (temperature exceeding 38 degrees Celsius), hypoxemia (oxygen saturation less than 90% on room air or the requirement of supplemental oxygen), tachypnea (respiratory rate exceeding 24 breaths/minute),[14] tachycardia (heart rate exceeding 124 beats per minute),[14] and hypotension (systolic blood pressure less than 90 mm Hg or the requirement of vasopressors). The patients' clinical course, treatments, and laboratory values were obtained either from the patient by phone (if remained outpatient), our electronic medical records, or records that were provided either electronically or by phone when we were in contact with the managing teams at outside hospitals. Laboratory values from outside hospitals with potentially variable detection methods or units that could not be confirmed were excluded from analysis. Acute kidney injury (AKI) was defined as a greater than 20% increase in creatinine from baseline; acute respiratory distress syndrome (ARDS) was defined by the Berlin criteria[15]; shock was defined as requiring vasopressors; transaminitis was defined as a greater than 3-fold increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) from baseline; and coinfection was defined as the presence of bacteria, virus, or fungus in any respiratory, blood, stool, urine, or bodily fluid specimen collected during the course of COVID-19, regardless of the pathological significance. Patients were followed until death or study end (May 29, 2020).

This study was approved by the Columbia University Institutional Review Board.

2.3 | Treatment protocols

Initially, our center's protocol for the treatment of lung transplant patients who tested positive for SARS-CoV-2 included hydroxychloroquine (600 mg BID for the first 2 doses followed by 400 mg daily for 4 days) plus azithromycin (500 mg for the first dose followed by 250 mg daily for 4 days) if low risk for QT interval prolongation. However, later in the study period, hydroxychloroquine and azithromycin were no longer recommended when negative data emerged.[16,17] Remdesivir (200 mg for the first dose followed by 100 mg daily for 4 days or 9 days) could be obtained through enrollment in a clinical trial (if criteria met) or later in the study period

through compassionate use or emergency authorization use. Patients were also eligible for enrollment in a blinded, randomized controlled trial of convalescent plasma later in the study period. When possible, efforts were always made to enroll patients in clinical trials. After initially avoiding high-dose steroids due to lack of efficacy and concern for delayed viral clearance in earlier data,[18] they were included in our protocol later in the study period following several severe cases and fatalities in our patients. Steroids were augmented only for patients in the hyperinflammatory phase of COVID-19 with evidence of cytokine release syndrome (elevated or rising CRP, ferritin, D-dimer, and/or LDH) and progressively worsening respiratory status (increasing infiltrates on chest x-ray and worsening oxygenation), beyond 3 to 5 days of symptom onset. Prednisone (or methylprednisolone equivalent) was increased to 1 mg per kg (to a maximum dose of 100 mg) every 8 hours for 3 days, then 1 mg per kg every 12 hours for 3 days, then 1 mg per kg once daily for 3 days, followed by a taper by 10 mg per day every 2-3 days based on clinical response and other comorbidities. For patients who required mechanical ventilation or were rapidly progressing toward requiring mechanical ventilation, methylprednisolone was increased to 10-15 mg per kg per day for 3-5 days, followed by the same taper. Tocilizumab (400 mg in a single dose) was considered for patients with evidence of cytokine release syndrome who had a transient or lack of response to steroids. The cell-cycle inhibitor dose was reduced by half in mild to moderate cases of COVID-19 and stopped in severe cases. No change was made to the calcineurin inhibitor dose or target level. No change was made to our protocol for VTE prophylaxis in hospitalized patients.

2.4 | Statistical analysis

Statistical analysis was performed using Stata/SE version 15.1. Continuous variables were compared using the *t*-test, and categorical variables were compared using the chi-squared test.

3 | RESULTS

3.1 | Baseline characteristics

A total of 33 lung transplant patients tested positive for SARS-CoV-2 between March 19, 2020 and May 19, 2020. One patient, of whom we were informed of the positive SARS-CoV-2 test only after her death at an outside facility, was excluded from this study on the basis of complete lack of clinical information regarding her disease course. Of the 32 included patients, the median age at the time of diagnosis was 65 years (range: 25-77 years). Patients were 50% male and of Caucasian (50%), Hispanic (28%), and African American (22%) ethnicities. They had received a single lung transplant (53%) or a double lung transplant (47%) for interstitial lung disease (ILD) (47%), cystic fibrosis (CF)/non-CF bronchiectasis (25%), sarcoidosis (12.5%), chronic obstructive pulmonary disease (COPD) (12.5%), or pulmonary arterial hypertension (PAH) (3%). The median time from

transplant was 5.6 years (range: 7 weeks to 13 years). At the time of diagnosis, 69% of patients had bronchiolitis obliterans syndrome (BOS) grade 0, 13% had BOS grade 1, 6% had BOS grade 2, 3% had BOS grade 3, and 9% were transplanted too recently to have sufficient PFT data for classification. Prior to diagnosis, 84% of patients were taking mycophenolate mofetil or mycophenolic acid (52% at a total dose of less than 2000 mg of mycophenolate mofetil or equivalent per day), 13% were taking azathioprine (50% at a dose of less than 150 mg daily), and 1 patient (3%) was not taking a cell-cycle inhibitor due to active malignancy. All patients were taking calcineurin inhibitors (75% tacrolimus and 25% cyclosporine A). All patients were taking prednisone (78% at a dose of less than 10 mg daily). Over half of patients (53%) were taking azithromycin for BOS. In the 3 months prior to diagnosis, 1 patient had received basiliximab (for induction at the time of transplant), 1 patient had received rabbit antithymocyte globulin (rATG) for treatment of acute cellular rejection, 1 patient had received antibody-depletion therapy (carfilzomib, rituximab, and bortezomib) and a steroid pulse (as defined at our center as methylprednisolone 10 mg/kg daily for 3 days), and 8 patients (25%) had received a steroid taper (as defined at our center by an increase in prednisone dose from baseline for 10 to 14 days).

Patients' comorbidities at baseline included chronic kidney disease (CKD) (66%, including 2 patients on dialysis), hypertension (56%), diabetes (44%), obesity (25%), heart disease (19%), and active malignancy (3%).

Median follow-up time for all patients was 44 days (range: 2-57 days). Median follow-up time for patients who survived to study end was 53 days (range: 10-71 days).

Baseline characteristics of patients with mild, moderate, and severe COVID-19 are reported in Table 1. No statistically significant differences were detected among the groups.

3.2 | Clinical presentation

Patients reported symptoms for a median duration of 4 days prior to SARS-CoV-2 testing (range: 0-14 days). Symptoms reported at the time of SARS-CoV-2 testing included cough (66%), dyspnea (50%), fever (47%), and GI upset (44%). Abnormal vital signs reported at the time of SARS-CoV-2 testing included hypoxemia (41%), tachypnea (16%), hypotension (9%), and tachycardia (3%). Blood pressure was not recorded for 4 patients and heart rate and respiratory rate were not recorded for 1 patient at the time of testing, and these were analyzed as normal. One patient was already hospitalized for a non-COVID-19-related issue at the time of testing, 18 patients (67%) were admitted to hospital on the day of testing, and 8 patients (30%) were admitted between 1 and 14 days after outpatient testing. The initial SARS-CoV-2 test for 1 patient was negative prior to another resulting as positive the following day.

Of the 27 patients who were hospitalized, symptoms reported at the time of admission (or at the time of SARS-CoV-2 testing in the case of the already admitted patient) were cough (85%), dyspnea (74%), GI upset (48%), and fever (41%). Abnormal vital signs

TABLE 1 Baseline characteristics by COVID-19 severity

	Mild (n = 5)	Moderate (n = 14)	Severe (n = 13)	P-value
Age, median (IQR)	62 (51-65)	64.5 (51-68)	65 (47-72)	.91
Male sex (%)	3 (60)	7 (50)	6 (46)	.87
Ethnicity (%)				.62
Caucasian	4 (80)	6 (43)	6 (46)	
African American	0 (0)	4 (29)	3 (23)	
Hispanic	1 (20)	4 (29)	4 (31)	
Transplant indication (%)				.31
ILD	1 (20)	6 (43)	8 (62)	
COPD	1 (20)	3 (21)	0 (0)	
PAH	0 (0)	0 (0)	1 (8)	
Sarcoidosis	0 (0)	2 (14)	2 (15)	
CF and non-CF bronchiectasis	3 (60)	3 (21)	2 (15)	
Transplant type (%)				.80
Double	3 (60)	6 (43)	6 (46)	
Single	2 (40)	8 (57)	7 (54)	
Years since transplant, median (IQR)	7.4 (2-8.4)	5.1 (2.2-9.3)	5.7 (2.1-8)	.93
BOS stage (%)				.21
0	4 (80)	11 (79)	7 (54)	
1	0 (0)	2 (14)	2 (15)	
2	0 (0)	0 (0)	2 (15)	
3	1 (20)	0 (0)	0 (0)	
Not available	0 (0)	1 (7)	2 (15)	
Baseline IS regimen (%)				
Mycophenolate < 2000 mg per day	2 (40)	4 (29)	8 (62)	.57
Mycophenolate ≥ 2000 mg per day	3 (60)	6 (43)	4 (31)	
AZA < 150 mg per day	0 (0)	2 (14)	0 (0)	
AZA ≥ 150 mg daily	0 (0)	1 (7)	1 (8)	
No cell-cycle inhibitor	0 (0)	1 (7)	0 (0)	
Tacrolimus	4 (80)	11 (79)	9 (69)	.82
Cyclosporine	1 (20)	3 (21)	4 (31)	
Prednisone < 10 mg daily	5 (100)	10 (71)	10 (77)	.41
Prednisone ≥ 10 mg daily	0 (0)	4 (29)	3 (23)	
Azithromycin	1 (20)	9 (64)	7 (54)	.23
Recent IS augmentation (%)				
Basiliximab	0 (0)	1 (7)	0 (0)	.51
Steroid pulse	0 (0)	0 (0)	1 (8)	.47
Steroid taper	1 (20)	3 (21)	4 (31)	.82
rATG	0 (0)	0 (0)	1 (8)	.47
Antibody-depletion therapy	0 (0)	0 (0)	1 (8)	.47
Comorbidities (%)				
Hypertension	3 (60)	8 (57)	7 (54)	.97
CKD	2 (40)	9 (64)	10 (77)	.33
Heart disease	1 (20)	1 (7)	4 (31)	.29

(Continues)

reported at the time of admission (or at the time of SARS-CoV-2 testing in the case of the already admitted patient) included hypoxemia (67%), tachypnea (19%), hypotension (15%), and tachycardia (4%). Respiratory rate, heart rate, and blood pressure at the time of admission could not be confirmed for 1 patient at an outside hospital and were analyzed as normal.

TABLE 1 (Continued)

	Mild (n = 5)	Moderate (n = 14)	Severe (n = 13)	*P*-value
Diabetes	2 (40)	8 (57)	4 (31)	.38
Obesity	1 (20)	5 (36)	2 (15)	.46
Active malignancy	0 (0)	1 (7)	0 (0)	.51

Abbreviations: AZA, azathioprine; BOS, bronchiolitis obliterans syndrome; CF, cystic fibrosis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IQR, interquartile range; IS, immunosuppression; PAH, pulmonary arterial hypertension; rATG, rabbit antithymocyte globulin.

Of the hospitalized patients, 89% of patients had new infiltrates on chest x-ray on admission: 67% were bilateral infiltrates, 17% were infiltrates on the graft side only, 4% were infiltrates on the native side only (and 3 chest x-ray findings could not be confirmed). Median values of laboratory results obtained upon admission were as follows: white blood cell count (WBC) 4.1 × 10³/uL (IQR 2.2-6.4), lymphocyte count 0.4 × 10³/uL (IQR 0.3-0.7), creatinine (of patients not on dialysis at baseline) 1.6 mg/dL (IQR 1.2-2.2), AST 36 U/L (IQR 27-56), ALT 23 U/L (IQR 14-29), ESR 55 mm/hr (IQR 32-75), CRP 82 mg/L (IQR 62-113), ferritin 809 ng/mL (IQR 534-1376), high-sensitivity troponin 27 ng/L (IQR 13-71), IL-6 20 pg/mL (IQR 11-32), procalcitonin 0.22 ng/mL (IQR 0.14-0.64), and D-dimer 1.5 ug/mL (IQR 0.6-2.4).

The clinical presentation and median initial laboratory values of hospitalized patients with moderate and severe COVID-19 are reported in Table 2. Patients with severe COVID-19 were more likely to present with hypotension upon admission than patients with moderate COVID-19.

3.3 | Treatment

Of the 32 patients, 27 (84%) received hydroxychloroquine, 24 (75%) received azithromycin, 14 (44%) received augmented steroids, 6 (19%) received tocilizumab, 3 (9%) received remdesivir, and 2 (6%) were enrolled in the blinded, randomized controlled trial for convalescent plasma. Most patients treated with hydroxychloroquine (67%) and azithromycin (58%) received at least the standard course as per our protocol, and the remainder received reduced dosing or the dosing could not be confirmed. Three of the patients who were taking azithromycin thrice weekly for BOS continued such dosing throughout the disease

TABLE 2 Clinical presentation and initial laboratory values at hospital admission by COVID-19 severity

	Moderate (n = 14)	Severe (n = 13)	*P*-value
Days of symptoms prior to testing, median (IQR)	6.5 (3-7)	3 (0-5)	.15
Fever (%)	7 (50)	4 (31)	.31
Cough (%)	13 (93)	10 (77)	.24
Dyspnea (%)	11 (79)	9 (69)	.58
GI upset (%)	9 (64)	4 (31)	.082
Hypoxemia (%)	8 (57)	10 (77)	.28
Tachypnea (%)	2 (14)	3 (23)	.56
Tachycardia (%)	0 (0)	1 (8)	.29
Hypotension (%)	0 (0)	4 (31)	.025
WBC count, median (IQR)	3.9 (1.5-6.4)	4.3 (3.4-6.3)	.66
Lymphocyte count, median (IQR)	0.4 (0.3-0.6)	0.4 (0.1-0.8)	.67
AST, median (IQR)	34 (27-56)	37 (24-57)	.87
ALT, median (IQR)	24 (18-29)	15 (13-28)	.24
Ferritin, median (IQR)	796 (502-2092)	850 (613-1048)	.94
ESR, median (IQR)	67 (36-82)	46 (32-55)	.24
CRP, median (IQR)	67 (56-113)	97 (77-109)	.27
Procalcitonin, median (IQR)	0.18 (0.07-0.6)	0.27 (0.21-0.71)	.10
D-dimer, median (IQR)	1.9 (0.8-2.7)	0.7 (0.6-2.2)	.32
IL-6, median (IQR)	23 (11-32)	16 (11-23)	.64

Notes: Lymphocyte count, x10³/uL; D-dimer in ug/mL; ferritin in ng/mL; procalcitonin in ng/mL.
Abbreviations: ALT, alanine aminotransferase (U/L); AST, aspartate aminotransferase (U/L); CRP, C-reactive protein (mg/L); ESR, erythrocyte sedimentation rate (mm/hr); IL-6, interleukin-6 (pg/mL); IQR, interquartile range; WBC, white blood cell (x 10³/uL).

period. Of the 6 patients who received tocilizumab, the initial dose was 400 mg IV (with 1 dose not confirmed) and 3 of the patients received an additional dose of 200 mg or 400 mg IV 3-4 days later. Of the 14 patients who were treated with augmented steroids, 10 received an oral prednisone course as per our protocol, 5 received a steroid pulse as per our protocol (4 of whom had been treated with an oral prednisone course prior and 1 of whom had been treated with stress-dose hydrocortisone prior), 1 received methylprednisolone 125 mg IV q8h then a taper from 70 mg daily, 1 received methylprednisolone 30 mg BID for 5 days only, and 1 received stress-dose hydrocortisone followed by methylprednisolone 125 mg for 1 dose and then 40 mg every 8 hours.

Among hospitalized patients only, 74% received broad spectrum antibiotics upon admission and 85% received them at some point during the hospitalization. Antibiotic administration could not be confirmed for 4 patients at other hospitals.

The cell-cycle inhibitor was reduced or held in 88% of cases. The calcineurin inhibitor was not adjusted except for conversion from tacrolimus to cyclosporine A in 1 case due to seizures. Prednisone was reduced in only 1 case.

3.4 | Clinical outcomes

As of May 29, 2020, 5 patients (16%) remained at home, 27 patients (84%) had been hospitalized, 11 patients (34%) had been admitted to the ICU, and 10 patients (31%) had required mechanical ventilation. Of the patients who were intubated, the median time to intubation from admission was 3 days (range: 0-15 days). One patient was extubated, but was re-intubated 10 days later for hypoxemic respiratory failure and then died. By study end, the mortality rate of mechanically ventilated patients was 100%.

According to our classification system, 5 patients (16%) had mild COVID-19, 14 patients (44%) had moderate COVID-19, and 13 patients (41%) had severe COVID-19. In total, 11 patients (34%) died at a median time of 14 days from admission (range: 3-48 days). The causes of death included shock, cardiac arrest, multi-organ failure, and withdrawal of care, all secondary to COVID-19. Among the hospitalized cohort who had survived as of May 29, 2020 (16 patients), 14 (87.5%) were discharged and 2 (12.5%) were still admitted. Of the patients who were discharged, the median length of stay in hospital was 13 days (range: 6-48 days).

Among all lung transplant patients, COVID-19-related complications included: AKI (63%), transaminitis (31%), shock (31%), ARDS (25%), neurological events (25%), arrhythmias (22%), and venous thromboembolism (9%). Neurological events included: seizure, altered mental status, hallucinations, loss of brainstem reflexes, migraine, and delirium. Coinfections were documented in 15 patients (47%). Respiratory coinfections included *K. pneumoniae, M. morganii, E. faecalis,* MRSA, MSSA, *P. aeruginosa,* and *C. albicans.* Of note, coinfections with other respiratory viruses could not be confirmed as our

TABLE 3 Clinical course by COVID-19 severity

	Moderate (n = 14)	Severe (n = 13)	*P*-value
Complications (%)			
AKI	7 (50)	13 (100)	.003
Arrhythmias	3 (21)	4 (31)	.58
VTE	1 (7)	2 (15)	.50
Transaminitis	1 (7)	9 (69)	<.001
Neurological events	2 (14)	6 (46)	.07
Coinfection	7 (50)	8 (62)	.55
Required mechanical ventilation (%)	0 (0)	10 (77)	.001
Died (%)	0 (0)	11 (85)	<.001
Peak WBC count, median (IQR)	7 (4.9-12.1)	15.8 (6.9-29)	.019
Nadir lymphocyte count, median (IQR)	0.4 (0.29-0.66)	0.09 (0.02-0.31)	.006
Peak ESR, median (IQR)	70 (43-110)	54 (43-79)	.80
Peak CRP, median (IQR)	107 (70-165)	198 (159-266)	.010
Peak ferritin, median (IQR)	1349 (631-2165)	2853 (1308-4766)	.12
Peak IL-6, median (IQR)	47 (27-60)	197 (43-315)	.09
Peak procalcitonin, median (IQR)	0.24 (0.13-0.87)	0.89 (0.27-2.1)	.067
Peak D-dimer, median (IQR)	2.1 (0.7-2.6)	8.6 (3.8-20)	.004

Notes: Lymphocyte count, x10^3/uL; D-dimer in ug/mL; ferritin in ng/mL; procalcitonin in ng/mL.
Abbreviations: AKI, acute kidney injury; CRP, C-reactive protein (mg/L); ESR, erythrocyte sedimentation rate (mm/hr); IL-6, interleukin-6 (pg/mL); IQR, interquartile range; VTE, venous thromboembolism; WBC, white blood cell (x10^3/uL).

center was unable to obtain the multiplex PCR for respiratory pathogens during the outbreak. Two patients had positive blood cultures (1 positive for *K. pneumonia*, 1 positive for *S. hominis*). Three patients had detectable cytomegalovirus in the blood. Certain coinfections were not considered pathogenic and did not require treatment. Certain complications could not be confirmed for 4 patients located at outside hospitals and were analyzed as absent.

Median values of peak laboratory results obtained during hospitalization were: WBC 10.8 × 10³/uL (IQR 6.1-17.1), creatinine (of patients not on dialysis at baseline) 2.5 mg/dL (IQR 1.4- 3.7), AST 58 U/L (IQR 40-175), ALT 35 U/L (IQR 27-155), ESR 55 mm/hr (IQR 43-96), CRP 159 mg/L (IQR 92-208), ferritin 1459 ng/mL (873-3252), high-sensitivity troponin 69 ng/L (IQR 16-97), IL-6 50 pg/mL (IQR 32-197), procalcitonin 0.42 ng/mL (IQR 0.18-1.1), and D-dimer 2.6 ug/mL (IQR 0.9-4.8). The median value of nadir lymphocyte counts during hospitalization was 0.3 × 10³/uL (IQR 0.1-0.4).

Clinical outcomes and median peak and nadir laboratory values during admission are reported for hospitalized patients with moderate and severe COVID-19 in Table 3. For patients who received tocilizumab, the peak IL-6 level prior to drug administration was analyzed. Compared to patients with moderate COVID-19, patients with severe COVID-19 were significantly more likely to develop AKI
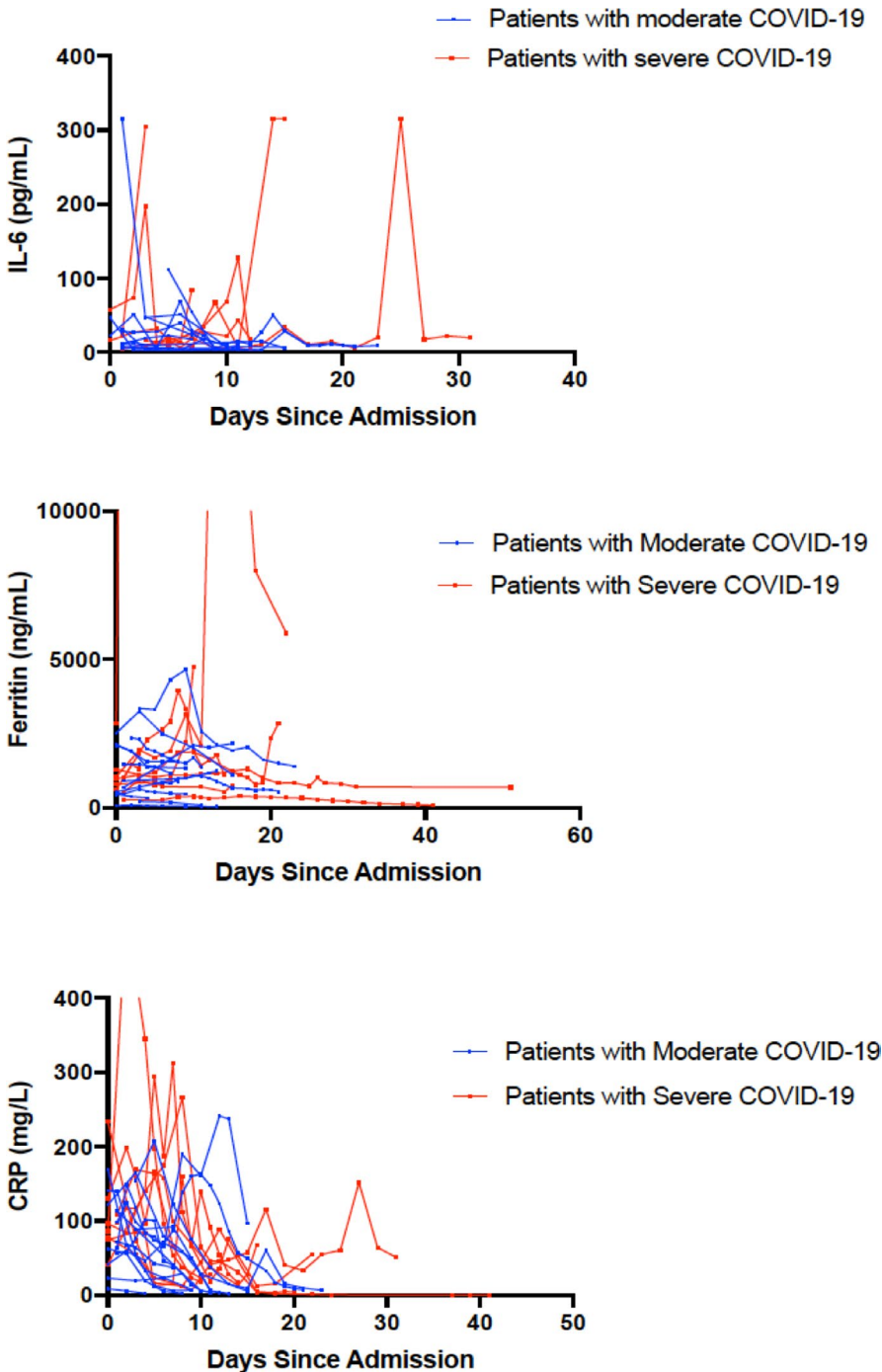

FIGURE 1 Trends of IL-6, ferritin, and CRP levels of patients with moderate and severe COVID-19 during admission

and transaminitis. They also had significantly higher peaks of WBC count, CRP, and D-dimer levels, and significantly lower nadir lymphocyte counts than patients with moderate COVID-19.

The trends of CRP, ferritin, and IL-6 levels of patients with moderate and severe COVID-19 are displayed in Figure 1. In general, CRP and IL-6 levels appear to be higher in patients with severe disease. The difference in ferritin levels between the 2 groups is less discernable.

Fifteen patients were treated either with steroid augmentation or tocilizumab. Of the 6 patients who received tocilizumab, 5 received concomitant steroid augmentation. Of these 15 patients, 6 (40%) improved to discharge, 2 (13%) were still admitted by study end, and 7 (47%) died. Three patients received remdesivir during the study period. Of these patients, 0 died, 2 improved to discharge, and 1 was still admitted by study end.

Ten patients had repeat SARS-CoV-2 swabs sent more than 5 days from the initial positive swab. Five of these patients had a repeat SARS-CoV-2 swab that remained positive a median of 21 days after the initial swab (range: 6-42 days). One of these 5 patients then had a SARS-CoV-2 swab that was indeterminate 45 days after the initial swab. Another 5 of the 10 patients had a repeat SARS-CoV-2 swab that was negative a median of 35 days after the initial swab (range: 12-57 days). One of these 5 patients then had another positive SARS-CoV-2 swab on the day after the negative swab, which was 18 days after the initial swab.

4 | DISCUSSION

The goal of this study was to report the impact of COVID-19 on lung transplant recipients. Our program has performed 65-85 lung transplants per year since 2015 and currently follows approximately 550 lung transplant recipients. In total, we identified and were able to collect clinical information on 32 of our patients who tested positive for SARS-CoV-2 between March 19, 2020 and May 29, 2020. Of this cohort, the hospitalization rate was 84%, the mechanical ventilation rate was 31%, and the mortality rate was 34%.

We did not identify any demographic data that seemed to be associated with disease severity, unlike prior work that found a significant correlation between disease severity and age, male gender, and ethnicity.[14,19,20] The fact that the majority of the patients affected were transplanted for ILD likely reflects the high prevalence of the disease in our transplant population, as underlying disease type did not correlate significantly with disease severity. Notably, we did not find a significant association between BOS grade and disease severity, although BOS grade 3 was underrepresented in this study, perhaps due to early social-distancing measures taken by these vulnerable patients. We also did not find that patients taking higher doses of immunosuppression at baseline developed more severe disease, although the only patients in this cohort who received thymoglobulin, antibody-depleting therapy, and high-dose steroids within the preceding 3 months did develop severe disease. Although no comorbidity commonly found in our patient population was significantly associated with more severe disease, this is likely due to the small sample size. Consistent with prior work,[21-23] we did find a high frequency of CKD, heart disease, diabetes, and obesity among patients with moderate or severe COVID-19.

Not surprisingly, patients who presented to hospital with hypotension were more likely to have severe COVID-19. During the course of the disease, patients with severe COVID-19 appeared to have higher peak CRP, D-dimer, ferritin, and IL-6 levels than patients with moderate COVID-19. The CRP and IL-6 levels over time did appear to be generally higher in patients with severe disease than patients with moderate disease, as well. This suggests that these inflammatory makers are likely a reflection of the presence of immune dysregulation in severe COVID-19,[24] and trending these markers (particularly CRP, D-dimer, and IL-6) in lung transplant patients with COVID-19 could assist with prognostication of disease.

At 84% and 34%, respectively, the hospitalization and mortality rates of lung transplant patients with COVID-19 are much higher than those of the general population of New York City,[1] and also higher than those of other solid organ transplant recipients.[7,9] More specifically, the mortality rate of patients who required mechanical ventilation was 100%. The time to intubation from admission to hospital ranged from 0 to 15 days, which reflects the 2 types of presentations of severe COVID-19 we observed in our patients: immediate and delayed onset. Regardless of the duration of time to onset, the survival from severe disease is very low. No treatment demonstrated particular efficacy, although larger and longer term studies are required to address this more definitively. It is possible that the risks of certain therapies, such as hydroxychloroquine and high-dose steroids, could have outweighed the benefits.

As a small, retrospective case series, this study is limited in its ability to detect significant differences in baseline characteristics, clinical presentations, laboratory data, or outcomes among lung transplant patients with mild, moderate, and severe COVID-19, or make meaningful conclusions with regard to prognostic markers or effective therapies. It is also possible that some of our patients with mild symptoms or positive SARS-CoV-2 tests performed at outpatient facilities did not contact our program within the study period. We may have underestimated our mild COVID-19 cohort due to this reporting bias. However, our study does provide the largest case series to date of lung transplant patients affected by COVID-19 and may guide lung transplant clinicians in patient management and counseling about the prognosis of COVID-19. Further studies will be required to assess longer term outcomes and, ultimately, the impact of COVID-19 on graft function.

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