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Clinical characteristics, management practices, and outcomes among lung transplant patients with COVID-19

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allograft dysfunction;
chronic kidney disease;
SARS-CoV-2;
survival

BACKGROUND: There are limited data on management strategies and outcomes among lung transplant (LT) patients with Coronavirus disease 2019 (COVID-19). We implemented management protocols based on the best available evidence and consensus among multidisciplinary teams. The current study reports our experience and outcomes using this protocol-based management strategy.

METHODS: We included single or bilateral LT patients who tested positive for SARS-CoV-2 on nasopharyngeal swab between March 1, 2020, to December 15, 2020 (n = 25; median age: 60, range 20-73 years; M: F 17:8). A group of patients with Respiratory Syncytial Virus (RSV) infection during 2016-18 were included to serve as a comparator group (n = 36).

RESULTS: As compared to RSV, patients with COVID-19 were more likely to present with constitutional symptoms, spirometric decline, pulmonary opacities, new or worsening respiratory failure, and need for ventilator support. Patients with SARS-CoV-2 infection were less likely to receive a multimodality treatment strategy, and they experienced worse post-infection lung function loss, functional decline, and three-month survival. A significant proportion of patients with COVID-19 needed readmission for worsening allograft function (36.4%), and chronic kidney disease at initial presentation was associated with this complication. Lower pre-morbid FEV_1 appeared to increase the risk of new or worsening respiratory failure, which was associated with worse outcomes.

Overall hospital survival was 88% (n = 22). Follow-up data was available for all discharged patients (median: 43.5 days, range 15-287 days). A majority had persistent radiological opacities (19/22, 86.4%), with nearly half of the patients with available post-COVID-19 spirometry showing > 10% loss in lung function (6/13, median loss: 14.5%, range 10%-31%).

CONCLUSIONS: Despite similar demographic characteristics and predispositions, LT patients with COVID-19 are sicker and experience worse outcomes as compared to RSV. Despite the availability of newer therapeutic agents, COVID-19 continues to be associated with significant morbidity and mortality.

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The emergence of Coronavirus disease 2019 (COVID−19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS−CoV−2), has caused significant morbidity and mortality across the world. The SARS−CoV−2 virus, while being highly infectious, does not have a high fatality rate among young and otherwise

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healthy people.[1] In contrast, its clinical manifestations are much more severe for older people and those with significant comorbidities.[2]

COVID-19 progresses in at least two well-defined stages, namely an early phase comprising of rapid viral replication presenting with fever and upper respiratory tract (URT) symptoms, with or without pulmonary or lower respiratory tract (LRT) involvement, and among a small sub-set of patients, systemic hyper-inflammation that causes multiorgan dysfunction.[3] The risk of respiratory failure is estimated to be between 5% to 15%, with a minority of patients progressing to acute respiratory distress syndrome (ARDS), multiorgan failure (MOF), and death.[4,5] While the overall clinical presentation and course have been fairly consistent across different geographic regions, climatic conditions, and healthcare systems, individual patient outcomes have been highly variable and difficult to predict. In patients with significant comorbidities, including those on immunosuppressive drugs, the consequences of COVID-19 have generally been worse.[5,6] While a weakened immune system may increase the risk of acquiring infection and developing pulmonary involvement, something well described with other community-acquired respiratory viruses (CARV), it is unclear if the immunosuppressive medications provide any protection against the systemic hyper-inflammation.[7]

Despite the higher risk of severe disease, the management strategy among patients with solid organ transplantation (SOT) has generally been similar to the general population. Moreover, the impact of SARS-CoV-2 infection may not be equivalent among all types of SOT. Specifically, patients with lung transplantation (LT) are likely to be more vulnerable, by virtue of the allograft itself being the target of the SARS-CoV-2.[6] However, outcomes for this specific population are not well understood, and best practices for managing COVID-19 in these patients have not been established. As an example, lung transplant patients often display significant clinical deterioration after infection with common CARVs such as respiratory syncytial virus (RSV). In normal hosts, RSV infection runs a relatively benign course; however, in lung transplant patients, its more severe course requires specific treatment protocols designed to mitigate the functional decline of the allograft. Our experience managing CARV infection in transplanted patients, therefore, offers a basis for comparison of both clinical outcomes and treatment protocols for SARS-CoV-2 infection.

At the onset of the pandemic, the lung transplant program at the University of Texas Southwestern Medical Center developed a management protocol for COVID-19 based on the consensus among multidisciplinary teams and the best available evidence. The treatment strategies were modeled on our management protocols for other CARV infections.[8-10]

The current study aims to report our experience in managing COVID-19 among LT patients in a protocolized manner over the last nine months. We sought to determine how the presentation and course of COVID-19 may differ from another CARV infection, namely, RSV. We also evaluate outcomes beyond the hospital admission and describe their post-discharge course.

Methods

This was a single-center retrospective chart review study approved by the UT Southwestern Medical Center Institutional Review Board (# STU-2020-1400).

Study groups

We queried the lung transplant database for all single or bilateral LT patients who tested positive for SARS-CoV-2 on a nasopharyngeal swab. The swabs were collected for symptomatic patients between March 1, 2020, and December 15, 2020, and tested for the SARS-CoV-2 virus using the quantitative polymerase chain reaction (PCR) assay. This assay targets the nucleocapsid and RdRp genes of the novel Coronavirus using the Abbott Alinity m SARS-CoV-2 assay, which received Emergency Use Authorization by the United States Food and Drug Administration for nasopharyngeal and nasal specimens. This test was validated by the UT Southwestern Medical Center Molecular Diagnostics Lab, Dallas, Texas, and the limit of detection of the assay was 100 copies/mL.

The protocol for testing for SARS-CoV-2 was preformulated and agreed upon by the lung transplant program. Patients were tested for SARS-CoV-2 if they presented with typical respiratory symptoms such as cough or dyspnea or separate constitutional complaints, including fatigue, malaise, or myalgias. While several asymptomatic patients with LT underwent pre-procedure screening for SARS-CoV-2 during this period per the institutional protocols, none of the screening swabs were positive. Patients with respiratory symptoms were classified as having URT involvement if the symptoms were limited to rhinitis, cough, or pharyngitis. In contrast, LRT involvement was represented by productive cough, wheezing, shortness of breath, a decline in spirometry, and opacities on a chest x-ray or computed tomography. The finding of peripheral oxygen saturations $< 90\%$, resting $PaO_2 < 55$ mmHg on room air, or $PaCO_2 > 45$ mm Hg was diagnosed as acute respiratory failure. An increase in home oxygen requirement or worsening of PaCO2 from baseline hypercapnia signified acute on chronic respiratory failure.

We also included patients with RSV infection diagnosed during 2016 to 2018 to serve as a comparator group ($n = 36$). None of these patients had COVID-19 at the time of study inclusion.

Management of COVID-19

In early March 2020, the lung transplant team at the UT Southwestern Medical Center put in place a proactive mitigation strategy as follows to reduce the infection risk-

1. Regular patient communications regarding the evolving situation with Coronavirus pandemic.
2. Emphasis on the use of face masks, hand hygiene, and social distancing.
3. Transition to virtual clinic visits unless in-person visit clinically indicated.

The management of patients with COVID-19 was protocolized early in the pandemic based on the best available evidence, expert guidance, and consensus among the multidisciplinary members of the lung transplant team (Table 1). While the management

Table 1 Management Protocol for Lung Transplant Patients With SARS-CoV-2 Infection

General Care
- Aerosol and contact isolation and precautions for 28 days from symptom onset
- Hold cell-cycle inhibitors till deemed to be recovered (2 weeks after symptom onset, gradually resume thereafter)
- Self-proning: Alternate every 2 hours between a prone and supine position during the day and sleep in a prone position at night, as tolerated
- Monitor symptoms, spirometry, laboratory studies and radiology (for hospitalized patient); advance to next level for any worsening

Level I

Patients with URT symptoms with or without constitutional symptoms, but no LRT symptoms or evidence of allograft dysfunction and qualified for bamlanivimab infusion
- Bamlanivimab infusion at the outpatient infusion center
- Prednisone taper, starting at 60 mg daily. Reduce dose by 25% every 3-5 days to the maintenance dose of 0.1 mg/kg/day
- Empiric course of antibiotic. Consider amoxicillin/clavulanate acid or levofloxacin for 7-14 days till symptom resolution

Level II

Patients with URT symptoms with or without constitutional symptoms but no LRT symptoms or evidence of allograft dysfunction, and unable to qualify for bamlanivimab infusion
- Admission to dedicated COVID units
- Blood and respiratory cultures at admission
- Remdesivir 200 mg IV on day 1 followed by 100 mg daily for 4 days. Check CT chest after 5th dose; extend therapy to complete 10 days among patients with parenchymal opacities consistent with COVID pneumonia.
- Check specific IgG antibody against SARS-CoV-2; if negative, proceed with convalescent plasma transfusion
- Check total IgG level. If levels< 400 mg/dL, replace with IVIG 500 mg/kg
- Prednisone taper as above
- Empiric course of PO antibiotic as above
- Prophylactic anticoagulation with unfractionated heparin or enoxaparin if not on chronic anticoagulation.

Level III

Patients with LRT *symptoms, or evidence of allograft dysfunction (based on symptoms with declined spirometry, supplemental oxygen needs, or opacities onimaging)*
- Remdesivir 200 mg IV on day 1 followed by 100 mg daily for 9 days.
- Check specific IgG antibody against SARS-CoV-2; if negative, proceed with convalescent plasma transfusion
- Check total IgG level. If levels< 400 mg/dL, replace with IVIG 500 mg/kg
- IV Methylprednisolone, starting at 10 mg/kg/day, every 24 hours for 3 doses among patients with objective findings of allograft dysfunction[a]. On day#4, initiate prednisone 40 mg daily and taper as above. Among patients with only subjective LRT symptoms, prednisone taper starting with 60 mg daily as above.
- Empiric course of IV antibiotics (Vancomycin and piperacillin/tazobactam or equivalent) to prevent bacterial superinfection while in the hospital. Discontinue vancomycin if nasal swab for methicillin-resistant staphylococcus aureus and blood cultures negative.
- If no contraindications, initiate systemic anticoagulation with unfractionated heparin infusion, or enoxaparin dosed at 0.7 mg/kg BID (among patients with eGFR>50 ml/ min).

IgG, Immunoglobulin G; IVIG, Intravenous Immunoglobulin; eGFR, estimated glomerular filtration rate; LRT, lower respiratory tract; URT, upper respiratory tract

[a]Shortness of breath with decline in spirometry, hypoxia, or radiological opacities consistent with COVID-19.

(*continued on next page*)

protocol continually evolved as the understanding of the COVID-19 disease improved and new data became available, early institution of multimodality pharmacological strategy remained the guiding principle-

1. Antiviral agent
2. Passive immunization
3. Corticosteroids to attenuate the post-viral alloimmune responses and hyper-inflammatory phase of the SARS-CoV-2 infection
4. Prophylactic broad-spectrum antibiotics.

Patients did not undergo bronchoscopy routinely.

Variables

All the data were obtained directly from the electronic medical records. The recorded variables included patient demographics (age, gender, and race), transplant indication, pre-transplant comorbidities, and type of immunosuppressive regimen at the time of SARS-CoV-2 infection. Apart from the presenting symptoms, we recorded pre-infection lung functions {forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1)}, laboratory abnormalities, radiological findings, and respiratory failure at diagnosis and during the course of illness. Various complications, namely, the need for admission to the intensive care unit (ICU), ventilator support (non-invasive or invasive), and rescue measures for refractory hypoxemia, were recorded. Finally, we reviewed the length of the hospital stay, the need for admission to a rehabilitation unit, hospital readmission for respiratory indications during the 30 days after discharge, post-infection lung functions, and survival. We also queried specifically for a significant loss of lung function (> 10%) from pre-infection baseline during the three-months after the SARS-CoV-2 infection.

Each patient chart was independently reviewed by a lung transplant nurse practitioner (LM) and a transplant pulmonologist (AB) to evaluate the lung function data and determine the diagnosis of chronic lung allograft dysfunction (CLAD) based upon the ISHLT criteria.[11] Discrepancies in the adjudicated timing and the determination of CLAD were reconciled.

Statistical analysis

Data were described as median with range and proportions as appropriate. We contrasted the characteristics and outcomes among patients with COVID-19 against those with RSV. The comparison was made using the Chi-square test and Mann-Whitney U test as appropriate. We also conducted comparative analyses among the patients with and without respiratory readmission as well as those with acute or acute on chronic respiratory failure

any time during their clinical illness using similar methodology. Statistical significance was considered at $p < 0.05$ (two-tailed only). The analysis was done using SPSS statistical software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.)

Results

Patient profile

During the study period, 25 LT patients (median age with range: 60, 20-73 years; M:F 17:8) were diagnosed with COVID-19. Most patients had restrictive lung disease as the transplant indication ($n = 17$) and underwent bilateral LT ($n = 23$). Two patients had combined liver-lung transplantation. Most patients were beyond the first year of LT ($n = 22$; median time since LT: 53.8, range: 5-113 months) and were symptomatic for a median of 3 days (range 0-10 days). Although the first patient with COVID-19 was diagnosed in March 2020, a majority of infections occurred between October and December ($n = 18$), with November alone accounting for nearly a third of all cases ($n = 8$, 32%). Diabetes mellitus ($n = 13$, 52%), chronic kidney disease ($n = 9$, 36%), coronary artery disease ($n = 7$, 28%), congestive heart failure ($n = 4$, 16%) and chronic atrial fibrillation ($n = 5$, 20%) were significant co-morbidities. More than a quarter of the patients had established CLAD ($n = 7$, 28%; obstructive CLAD: 3, restrictive CLAD: 2, and mixed phenotype: 2).

A majority of patients reported LRT symptoms at presentation ($n = 22$, 88%), while URT symptoms alone were unusual ($n = 2$). Constitutional symptoms such as fever, headache, and myalgias were common ($n = 18$, 72%). History of contact with a sick family member was endorsed by most patients ($n = 14$, 56%). Among the patients with available spirometry data ($n = 14$), more than half had 10% or more decline (57.1%) from baseline. Opacities were present on chest radiographs among 11 patients (44%) at admission, while four additional patients developed opacities during the hospital stay. More than a third of the study group developed acute or acute on chronic respiratory failure ($n = 9$, 36%) during the primary admission. Blood cultures collected at the time of admission were negative among all patients. At least one respiratory culture was available among 8 patients only (tracheal aspirate among 6 patients on invasive ventilator and 2 patients with acceptable sputum samples). Among these, two samples were positive for *Pseudomonas aeruginosa* (both sensitive to piperacillin/tazobactam), and one was positive for *Aspergillus fumigatus* (treated with Posaconazole).

Management

Nearly all patients except one treated with bamlanivimab, were hospitalized. Various pharmacotherapeutic and respiratory support strategies used are presented in Figure 1. All patients received a combination of corticosteroids and broad-spectrum antibiotics. Remdesivir was used for 17 patients (median time to initiation from symptom onset: 3.5 days, range 1-8 days) during the primary admission for COVID-19 with most patients treated for 5 days ($n = 9$, 53%; median duration of treatment: 5 days; range 0-10 days). Passive immune augmentation was utilized for 16 patients (convalescent plasma: $n = 14$; median time to initiation: 4 days, range 1-8 days) and intravenous immunoglobulin: $n = 3$).

Among the nine patients with new or worsening respiratory failure, the majority needed high flow oxygen ($n = 7$). Four patients needed non-invasive ventilator support, while three were intubated and admitted to the intensive care unit for ARDS. Two of the three intubated patients needed neuromuscular blockade (paralytic) agents, prone positioning, and inhaled nitric oxide. One patient with refractory hypoxemia (PaO_2/FiO_2 ratio < 50) along with MOF was treated with two doses of tocilizumab, 12 hours apart with a good response. Around 24 hours after the completion of the second dose of tocilizumab, this patients' acute phase reactants started to trend down. At 48 hours, hypoxemia started to improve, and by 72 hours PaO_2/FiO_2 ratio had improved to > 100. Other organ functions also improved concomitantly. He was eventually extubated on day#16 and transferred out of the ICU on day#25.

Outcomes

Figure 2 summarizes the clinical course of the study group in a flowchart. Two patients died during the initial hospitalization for COVID-19. While both of these patients developed respiratory failure, neither progressed to ARDS or MOF. In accordance with family's wishes, both patients were electively transitioned to comfort care due to significant comorbidities (severe aortic stenosis with congestive heart failure, recalcitrant atrial arrhythmias, and delirium in one patient and advanced dementia in the other). In contrast, two patients who needed rescue strategies for refractory hypoxemia survived (one patient remains hospitalized since their primary admission at the time of this report). The median length of hospital stay was 6.5 days (range 1-49 days), and two patients needed admission to an inpatient rehabilitation unit for debility.

Among the discharged patients ($n = 21$) and the one treated outpatient, recurrence or worsening of respiratory symptoms requiring readmission was common (8/22, 36.4%; median time to readmission: 5.5 days among the discharged patients). Overall, a milder initial presentation appeared to increase the risk of readmission as indicated by fewer patients with parenchymal opacities at presentation (12.5% vs 57.1%) and need of respiratory support beyond the nasal canula (12.5% vs 50%) as well as shorter length of hospital stay (5.5 days vs 8.5 days), although none of these differences were statistically significant. The median duration of symptoms at diagnosis (2.5 days vs 3 days) and (time from LT (50.8 months vs 44.2 months; proportion of patients in the first year of LT: 12.5% vs 14.3%) were similar among patients with and without readmission. However, patients with chronic kidney disease stage 3 or worse (62.5% vs 14.3%; OR, 95% CI: 10, 1.26-79.34; $p = 0.02$) and higher median creatinine levels were more likely to

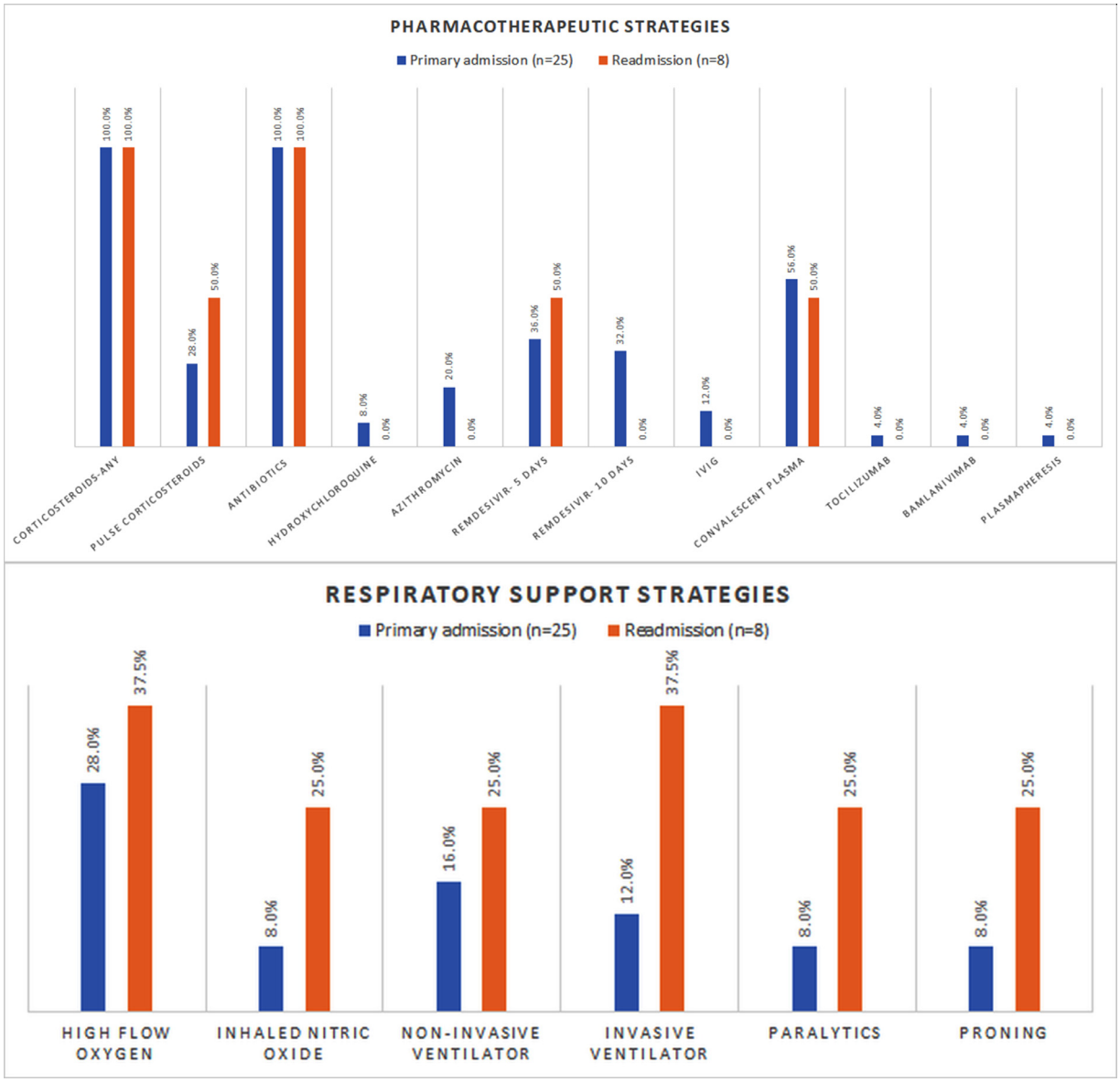

Figure 1 Bar diagram showing the proportion of patients with different pharmacotherapeutic (upper panel) and respiratory support (lower panel) strategies during the primary admission (n = 25, blue bars) and readmission (n = 8, orange bars). The proportion of patients treated with different pharmacotherapeutic approaches during readmission seemed to mirror those during primary admission, as reflected by the similar lengths of blue and orange bars. In contrast, a higher proportion of patients needed various respiratory support strategies during the readmission (taller orange bars). (Color version of figure is available online.)

need readmission. Figure 3 shows the timeline for the clinical course of illness (divided into four stages) among patients with readmission.

All patients who needed readmission developed post-COVID-19 opacities on imaging; five patients developed new respiratory failure (2/5 patients had developed respiratory failure and recovered during their primary admission as well), and three required mechanical ventilation. Apart from the supportive care, patients were treated with remdesivir (additional doses to complete ten days among three patients, and one patient was treated with remdesivir for the first time during the readmission), pulse corticosteroids (n = 4), and convalescent plasma among those with negative SARS-CoV-2 IgG (n = 4). Three of the four patients with positive serology for SARS-CoV-2 at the time of readmission had received convalescent plasma during the primary admission. A higher proportion of patients needed respiratory support interventions during the readmission (see Figure 1, lower panel). One patient needed tracheostomy for ventilator-dependent respiratory failure, and another one died due to infectious complications from secondary bacterial (*Pseudomonas aeruginosa)* pneumonia.

The profile of patients who developed new or worsening respiratory failure (acute or acute on chronic) during either admission is compared in Table 2. Patients with restrictive lung diseases as the transplant indication, worse pre-morbid FEV_1, and established CLAD appeared to be at a higher risk of this complication. A lower proportion of patients with respiratory failure were treated with remdesivir and convalescent plasma, although the difference did not

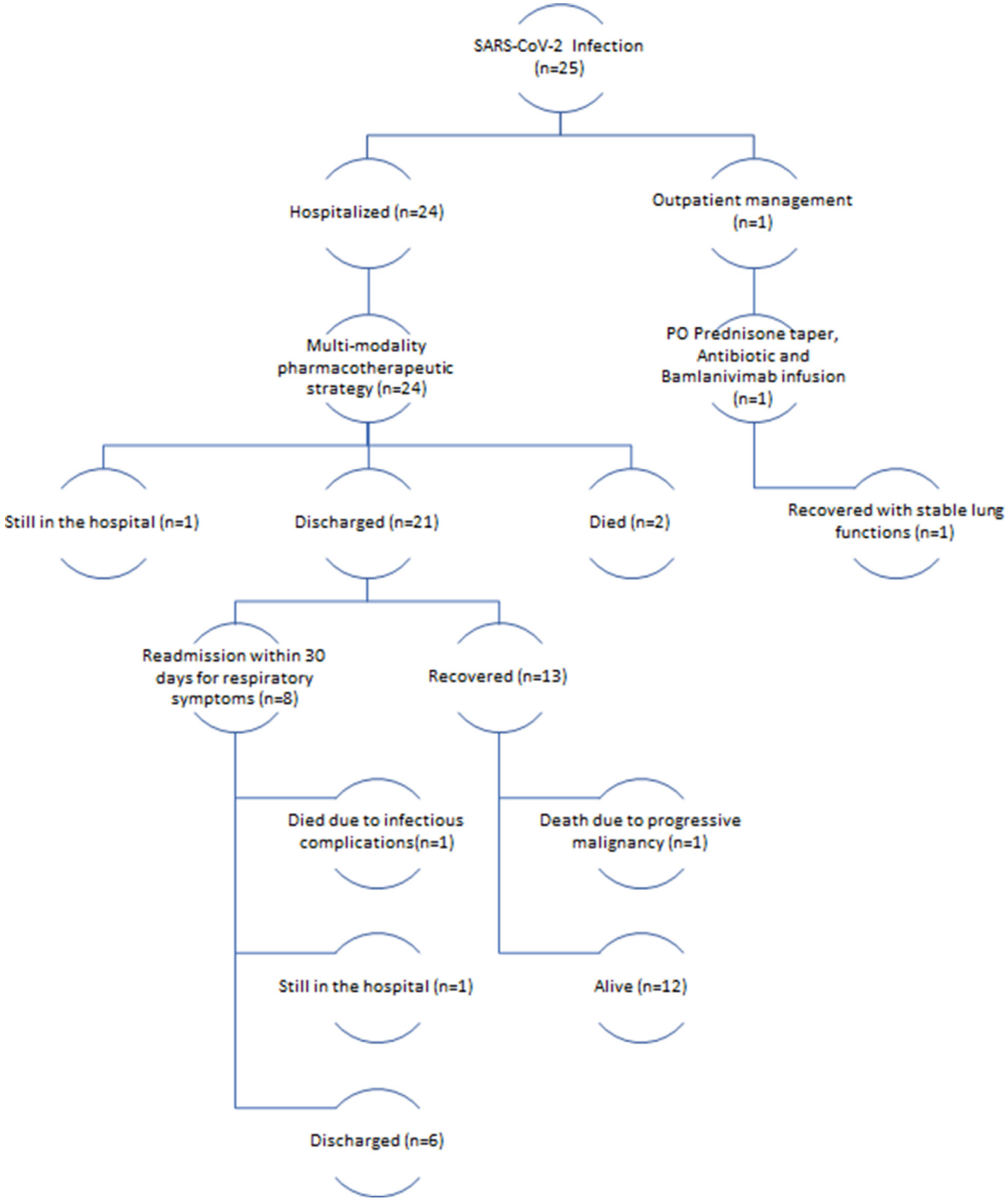

Figure 2 Flowchart showing the outcomes among lung transplant patients with SARS-CoV-2 infection.

achieve statistical significance. However, patients with respiratory failure had a significantly longer median time from the symptom onset to the initiation of remdesivir and convalescent plasma. Expectedly, respiratory failure was associated with worse morbidity and mortality.

Overall, hospital survival for the study group was 88% (n = 22, although two patients remain in the hospital at the time of this report). Follow-up data was available for all discharged patients (median length of follow-up: 43.5 days, range 15-287 days). A vast majority had persistent radiological opacities (19/22, 86.4%), predominantly affecting the lower lobes (Figures 4 and 5). Among the 13 patients with available post-COVID-19 spirometry (all studies done four weeks or more after the illness onset), six patients had > 10% loss in FVC or FEV_1 (median FVC or FEV_1 loss: 14.5%, range 10%-31%). Most patients reported worsening of functional status with median Karnofsky performance status of 70% (range 20%-80%). One patient with pre-COVID-19 diagnosis of oral squamous cell cancer died from progressive disease at four months.

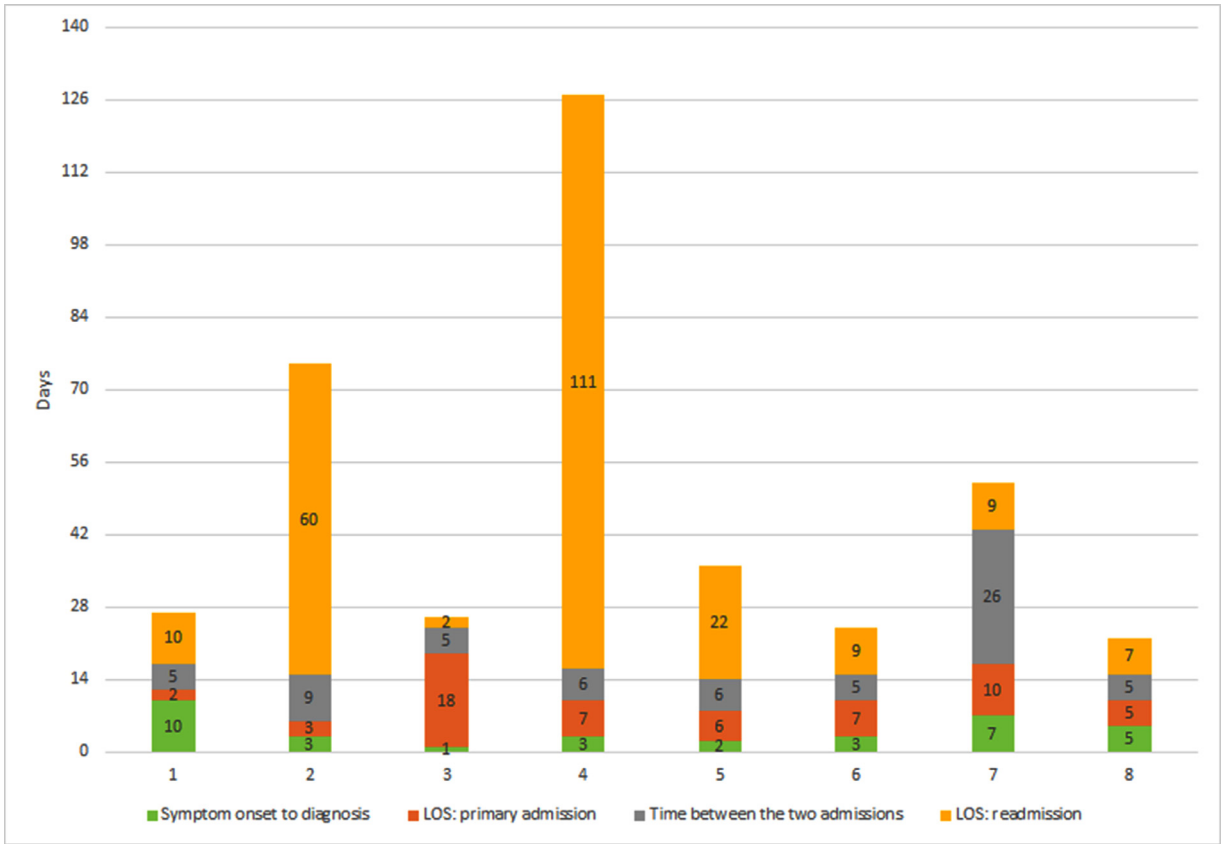

Figure 3 The timeline of the clinical course of patients with SARS-CoV-2 infection who needed readmission (n = 8). Number of days spent in each of the four phases are included in the bar diagrams.

Comparative analysis of patients with COVID-19 and RSV

A comparison of patients with COVID-19 and RSV is presented in Table 3. There were several pertinent differences, though some comparisons did not reach statistical significance. Patients with COVID-19 were further out from their transplant, although the pre-infection median lung function and the incidence of CLAD were similar. A majority of patients with both infections presented with LRT symptoms although those with COVID-19 were more likely to have constitutional symptoms and objective findings of pulmonary involvement as evidenced by spirometric decline, opacities on the radiograph, new or worsening respiratory failure, and a need for ventilator support. Despite this, patients with COVID-19 were less likely to receive the multimodality treatment protocol, including pulse corticosteroids. The outcomes such as the post-infection decline in lung functions and survival after COVID-19 tended to be worse.

Discussion

The current study reports our experience with the presentation and outcomes among LT patients with COVID-19. There is a scarcity of outcomes data among LT patients with COVID-19, and this is the second-largest series to emerge from the United States. The current analysis provides insights into outcomes among these patients, especially in the later months of the pandemic as some therapeutic options have begun to emerge. Further, the current analysis contrasts the course of SARS-CoV-2 infection against another respiratory viral infection, RSV, which is known to have significant implications for patients with LT.[12-15]

The monthly incidence of SARS-CoV-2 infection seemed to largely mirror the community spread in the United States.[16] Furthermore, the spread of SARS-CoV-2 does not appear to have the typical seasonal variation consistently seen among other CARV infections.[8] While there has been a sharp increase in cases in the more recent, cooler months, the warmer temperatures did not seem to provide the protection typically seen with other CARVs.[16] In fact, 20% of the cases in the current cohort occurred over the summer months.

The earlier series describing COVID-19 in LT patients from the United States[6,17,18] as well as from Spain,[19] Belgium[20] and France[21] reported markedly variable patient outcomes despite being from the same time period. The hospital outcomes in the largest case series from Spain were poor, with more than 80% of the patients developing respiratory failure and nearly 40% succumbing to the infection. Similarly, in New York, 34% of the LT patients with COVID-19 succumbed within 2 weeks of illness,[18] while the mortality rate was 25% in a series from Philadelphia.[17]

Table 2 Comparative Analysis of Characteristics Among Lung Transplant Patients With Acute or Acute on Chronic Respiratory Failure at Any Time After SARS-CoV-2 Infection

	Acute or acute on chronic respiratory failure			
Variable	Yes (n = 12)	No (n = 13)	Odds ratio (95% CI)	p value
Age	61 (20-73)	60 (26-71)		0.73
BMI at diagnosis (Kg/m^2)	26.5 (17-31)	27.1 (17.6-33.4)		0.5
Male gender	66.7%	69.2%	0.89 (0.17-4.78)	0.89
Non-Caucasian	41.7%	30.8%	1.61 (0.31-8.32)	0.69
Diabetes mellitus	41.7%	61.5%	0.45 (0.09-2.22)	0.43
Transplant Indication (%)				0.08
Restrictive	91.7	46.1		
Obstructive		30.8		
Suppurative	8.3	15.4		
Vascular		7.7		
Bilateral Transplant	91.7%	92.3%	0.92 (0.05-16.49)	1.0
Time since transplant (months)	65.7 (27-113)	25.7 (5-98)		0.09
Baseline FEV_1 before the infection (% of predicted)	56 (29-147)	78 (63-114)		0.02
Baseline FVC before the infection (% of predicted)	65 (43-114)	78 (54-105)		0.46
Co-morbid renal dysfunction[a]	41.7%	30.8%	1.61 (0.31-8.32)	0.69
Established CLAD	41.7%	15.4%	3.93 (0.59-26.11)	0.2
Duration of symptoms at diagnosis (days)	3 (0-7)	3 (1-10)		0.89
Lower respiratory tract symptoms at presentation	91.7%	84.6%	2.0 (0.16-25.4)	1.0
Spirometry decline of >10%	85.7% (n = 7)	28.6% (n = 7)	15.0 (1.03-218.3)	0.05
Parenchymal opacities on radiographs during either admission[b]	100%	61.5%		0.04
Lymphocyte count (X10^3/dL)[c]				
At admission	1.2 (0.4-2.94)	1.1 (0.6-1.6)		0.61
Lowest during admission	0.19 (0-0.46)	0.41 (0-1.16)		0.79
At discharge	0.39 (0.04-1.34)	0.9 (0.29-1.65)		0.25
Ferritin (mcgm/L)[c]				
At admission	131 (0.25-1187)	95 (36-400)		0.93
Lowest during admission	145 (56-2213)	112 (32-938)		0.79
At discharge	154 (56-2232)	128 (36-938)		0.79
C-reactive protein (mg/L)[c]				
At admission	7.3 (0-63.4)	5.0 (1.0-59.4)		0.5
Lowest during admission	2.75 (0-192.6)	2.45 (0.7-12.2)		0.84
At discharge	12.75 (0-192.6)	4.25 (0.4-12.2)		0.13
Lactate dehydrogenase (U/L)[c]				
At admission	219.5 (145-260)	221 (124-351)		0.89
Lowest during admission	271.5 (148-532)	214 (168-450)		0.88
At discharge	277 (151-600)	225 (173-473)		0.104
Serum Creatinine (mg/dL)[c]				
At admission	1.28 (0.8-2.3)	1.05 (0.63-1.4)		0.25
Lowest during admission	0.95 (0.38-3.07)	0.94 (0.56-1.4)		0.89
At discharge	1.07 (0.55-3.07)	1.03 (0.67-1.41)		0.77
Remdesivir	66.7%	76.9%	0.6 (0.1-3.5)	0.67
Time from symptom onset to Remdesivir initiation (days)	6 (2-14)	2.5 (1-7)		0.012
Convalescent plasma	58.3%	69.2%	0.62 (0.12-3.22)	0.69
Time from symptom onset to Convalescent plasma (days)	6 (4-23)	4 (1-7)		0.031
Pulse corticosteroids	58.3%	30.8%	3.15 (0.61-16.31)	0.24
Cumulative length of hospital stay (days)[d]	22 (2-18)	9 (0-20)		0.005
Need of ICU admission	50%	7.7%	12.0 (1.16-123.7)	0.03
Need of ventilator support	50%	None		0.005
Hospital survival (n = 23)[e]	70% (n = 10)	100%		0.07
Post-COVID-19 pulmonary opacities[f]	100% (n = 9)	69.2%		0.09

BMI, Body mass index; FEV_1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; ICU, Intensive care unit

[a]Defined as CKD-3 or higher;

[b]CT chest done among 9 patients with and 11 patients without ARF

[c]at the time of primary admission;

[d]Combined length of stay from the primary admission and readmission;

[e]Two patients in the respiratory failure group still in the hospital at the time of the report;

[f]After primary admission and readmission. Patients underwent CT chest during the post-discharge follow up visit after recovering from COVID-19

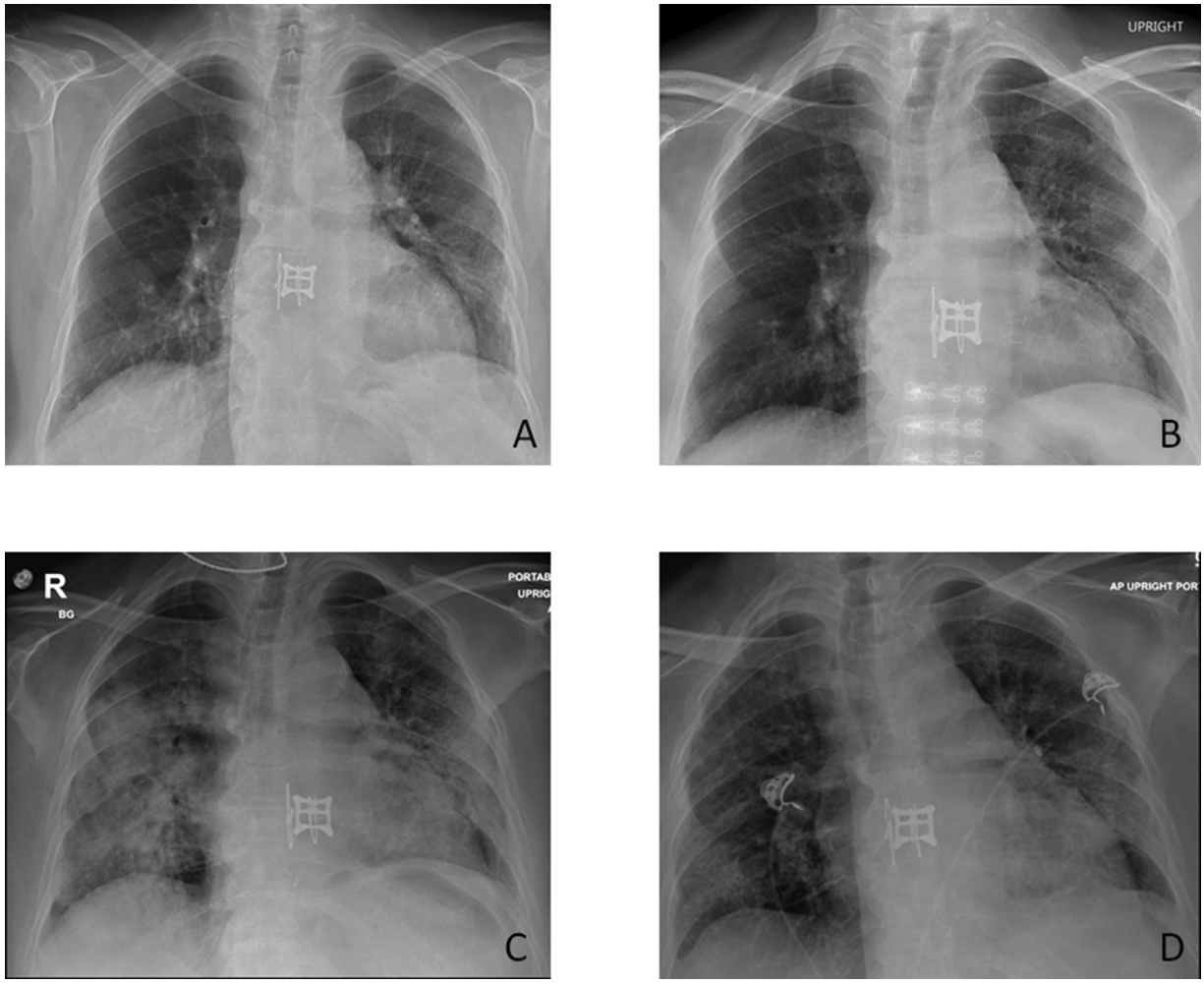

Figure 4 Serial chest radiographs of a 66/F bilateral lung transplant patient with COVID-19 infection. She presented with cough, sore throat and myalgias for 3 days. She had chronic kidney disease and creatinine peaked at 1.81 mg/dL during the illness. Chest radiographs was unremarkable at presentation (A). She was treated with remdesivir, oral prednisone taper, convalescent plasma and oral levofloxacin with improvement in her symptoms. She was discharged with stable spirometry and good oxygen saturations on room air after 6 days (B). She presented to the emergency room 8 days later with worsening shortness of breath and noted to be hypoxemic. She was admitted to the floor and started back on remdesivir, IV antibiotics and pulse corticosteroids. Over the next 48 hours, patient continued to worsen with increased oxygen needs and worsening opacities (C) culminating in mechanical ventilation, paralytics and prone positioning. She was continued on the same regimen and started to improve 3 days later with eventual extubation. Patient was weaned off oxygen although radiograph two weeks later showed overall much improved but persistent bilateral lower zone opacities (D).

Conversely, the outcomes from the Belgian series[20] appeared to be better, although it included only 10 patients. Finally, the multicenter French case series, consisting of 35 patients, among which 25 were hospitalized, reported the best survival to date of 85.7% (n = 30) at a median follow up of 50 days (41-56 days). In the current study, despite the significant hospital mortality, the pre-terminal events were different, with no deaths during the acute ARDS phase.[22] However, patients with COVID-19 experienced much worse morbidity than RSV. Despite similar demographic characteristics and predispositions, patients with COVID-19 were sicker at presentation, more likely to have LRT involvement, develop respiratory failure and require mechanical ventilation. Although the guiding principles behind management protocols for both COVID-19 and RSV were similar, the proportion of patients receiving the different components of the multimodality treatment were significantly lower with COVID-19. While this was predominantly due to lack of availability of effective therapies, the novelty of the virus mandated a cautious approach in our protocols such as with the use of high dose corticosteroids.

The three patients who died from COVID-19 had significant co-morbid illnesses apart from advanced CLAD. None of the deaths occurred from refractory hypoxemia related to ARDS during the acute phase of COVID-19. Whether this reflects the blunted hyper-inflammatory phase of COVID-19 among LT patients, a result of either their baseline immunosuppression[23] or the protocolized use of corticosteroids among these patients, needs further assessment. However, it is likely that early use of corticosteroids is effective in favorably modifying the course of illness. While the evidence favoring the beneficial role of corticosteroids in COVID-19 was first published in July 2020,[24] our

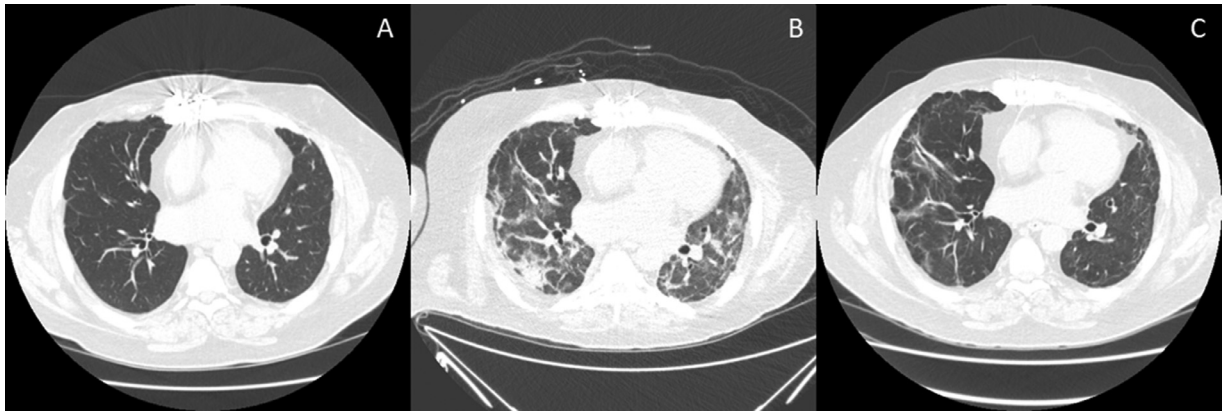

Figure 5 Serial CT chest images of 55/M liver-lung transplant patient with COVID-19. First image is from 1 month before the infection (A). He presented acutely ill with refractory hypoxemia and multiorgan dysfunction requiring mechanical ventilation, paralytics, inhaled nitric oxide and prone positioning. The second image shows parenchymal opacities during the active infection (B). He was treated with supportive care, corticosteroids taper, antibiotics and two doses of tocilizumab. He slowly improved and after a prolonged hospital stay, he was weaned off oxygen. His CT chest 6 months after infection showed bilateral reticular opacities (C) while spirometry showed an FEV1 loss of 15% from pre-infection baseline.

Table 3 Comparative Analysis of Characteristics Among Lung Transplant Patients With SARS-CoV-2 and RSV Infection

Variable	SARS-CoV-2 (n = 25)	RSV (n = 36)	Odds ratio(95% CI)	p value
Age	60 (20-73)	59 (14-80)		0.31
BMI at diagnosis (Kg/m^2)	26.8 (17-33.4)	25.9 (16.3-37.2)		0.89
Male gender	68%	61.1%	1.35 (0.46-3.97)	0.58
Hispanics	20%	8.3%	2.75 (0.59-12.77)	0.25
Hypertension	84%	83.3%	1.05 (0.26-4.18)	0.95
Diabetes mellitus	52%	38.9%	1.70 (0.61-4.78)	0.31
Transplant Indication (%)				0.52
Restrictive	68	50		
Obstructive	16	19.4		
Suppurative	12	25		
Vascular	4	5.6		
Bilateral Transplant	92%	77.8%	1.46 (0.98-2.17)	0.14
Time since transplant (months)	53.8 (5-113)	30 (1-135)		0.025
Baseline FEV_1 before the infection (% of predicted)	66.5 (29.2-147)	76 (17-121)		0.93
Baseline FVC before the infection (% of predicted)	69 (43-114)	75.5 (28-119)		0.89
Hypogammaglobinemia at presentation (<400 mg/dl)	12%	30.6%	0.31 (0.08-1.26)	0.09
Established CLAD	28%	25%	1.17 (0.37-3.7)	0.79
History of sick contact	60%	22.2%	5.26 (1.7-16.1)	0.003
Constitutional symptoms at presentation	72%	44.4%	3.21 (1.08-9.59)	0.04
Lower respiratory tract symptoms at presentation	88%	91.7%	0.67 (0.12-3.61)	0.64
Spirometry decline of >10%	57.1% (n = 14)	33.3% (n = 33)	2.67 (0.74-9.61)	0.19
Parenchymal opacities on radiographs	48%	22.2%	3.23 (1.06-9.81)	0.05
Proportion of patients hospitalized	96%	91.7%	2.18 (0.21-22.28)	0.64
Acute or acute on chronic respiratory failure	36%	11.1%	4.5 (1.2-16.9)	0.02
Need of ventilator support	24%	11.1%	2.52 (0.63-10.1)	0.18
Antiviral agent[a]	72%	100%		0.001
Passive immunity augmentation strategies[b]	68%	91.7%	0.19 (0.04-0.82)	0.03
Pulse corticosteroids (overall)	44%	91.7%	0.07 (0.017-0.3)	<0.001
Length of hospital stay during primary admission (days)	6.5 (1-49)	6 (3-88)		0.81
30-day readmission for respiratory indications	36.4% (n = 22)	9.4% (n = 35)	6.1 (1.4-26.46)	0.015
Post-infection lung function loss on spirometry >10%[c]	46.1%	25.7%	2.48 (0.66-9.34)	0.29
Three-month survival	88%	97.2%	0.21 (0.02-2.14)	0.29

FEV_1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; RSV, Respiratory syncytial virus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2;

[a]Represents Remdesivir for SARS-CoV-2 patients and Ribavirin inhaled (n = 33) or oral (n = 3) for RSV group;

[b]Represents convalescent plasma (n = 16)/ Bamlanivimab (n = 1) for SARS-CoV-2 patients and Palivizumab for RSV group

[c]Lung functions were conducted at least 4 weeks or more from the time of symptom onsetConstitutional symptoms included a combination of fever, chills, headache, and myalgias.

management protocol advocated for its use well before that and was based on our experience with other CARV infections among LT patients. Multiple studies and meta-analyses have since been published that firmly establish the role of corticosteroids among critically ill patients with COVID-19.[25-27] While it is unlikely that similar studies will be conducted among LT patients, the theoretical benefits of corticosteroid use extend beyond the attenuation of the hyper-inflammatory phase among LT patients. Perhaps importantly in this population, corticosteroid use was coupled with proactive utilization of passive immunization, prophylactic antibiotics, and antiviral agents (when available), strategies that might mitigate the potential risks associated with corticosteroid use and facilitate recovery. Of note, the use of empiric antibiotics among all patients was dictated by the novelty of the virus and the lack of published data regarding the frequency of bacterial superinfection among these patients. Besides, most patients (n = 17) were unable to provide respiratory specimen and were being treated with higher dose corticosteroids which could increase the risk of secondary bacterial infections. Regardless, the strategy of prophylactic antibiotic use should be weighed against the increased risk of multi-drug resistant nosocomial infections among these patients[28,29]

While the current study design does not allow assertions about efficacy, early and proactive use of corticosteroids seemed to improve the disease course regardless of the timing of presentation and severity of illness. We did not encounter a widespread increase in the number of opportunistic infections. The only patient who died of infectious complications had a long, complicated hospital course culminating in bacterial sepsis 10 weeks after the diagnosis. While expanding the use of high-dose corticosteroids for all symptomatic patients with COVID-19 may attenuate the risk of subsequent allograft dysfunction, it may increase the risk for other complications. We, therefore, favor continuing a measured approach towards the use of high-dose corticosteroids given the novelty and unique characteristics of the SARS-CoV-2 virus.

We found that a longer duration of symptoms before initiation of remdesivir and convalescent plasma was associated with new or worsening respiratory failure. Intriguingly, the duration of symptoms before the diagnosis was similar between the two groups (Table 2). In other words, initiation of therapies was delayed despite the confirmation of the diagnosis in some patients. This tended to occur during the earlier part of the pandemic when the availability of both of these agents was limited and took time to be arranged. While these findings indicate that a delay in initiating these agents may be associated with worse outcomes, larger studies are needed to confirm these findings. This is especially pertinent among immunocompromised patients, where passive immune augmentation may be more critical than immunocompetent patients. In fact, Salazar and colleagues reported on the time-sensitive nature of the efficacy of convalescent plasma (within 72 hours of symptom onset),[30] although this finding has not been replicated among other studies.

Another important finding from the current analysis relates to the 'delayed' allograft dysfunction necessitating readmission among several patients. We arbitrarily referred to the 'delayed' allograft dysfunction as new or worsening allograft function occurring beyond the first two weeks of clinical illness (onset of symptoms). Often, these patients presented with respiratory failure after discharge from the hospital, and their work up for alternate etiologies for allograft dysfunction was negative. The severity was highly variable, ranging from pauci-symptomatic new radiological opacities to refractory hypoxemia requiring intubation and mechanical ventilation (Figure 4). The clinical profile of these patients was largely indistinguishable from COVID-19 pneumonia- positive PCR, elevated inflammatory markers, and nodular ground glass pulmonary opacities.[31] However, half of the patients tested positive for antibodies against SARS-CoV-2 (n = 4), suggesting an alternate etiology for the decompensation. While this phenomenon has not been well described before, one of the patients in the series from Belgium appeared to have a similar presentation. This patient was initially managed in the outpatient setting but presented with new respiratory symptoms and ground glass opacities on CT chest.[20] In our experience, these patients respond well to the resumption of higher doses corticosteroids and supportive care. However, long-term impact on the allograft function remains a concern as all the patients had persistent pulmonary opacities on follow up imaging. We suspect that some of the patients with delayed allograft dysfunction had post-viral activation of alloimmune responses that are well described after other CARV infections and can be challenging to distinguish from COVID-19. It is important for transplant teams to be cognizant of this presentation. Additionally, patients with chronic kidney disease appear to be at a higher risk that may be related to factors such as a pro-inflammatory milieu among these patients,[32,33] conservative use of diuretics or maintenance of lower calcineurin inhibitors levels.

The current analysis provides useful insights into the adverse impact of COVID-19 beyond the early period which had not been previously reported. While early outcomes in the current series were encouraging, significant morbidity beyond the acute illness remains a concern. Apart from the need to further optimize the timing and modalities of early management, future studies need to evaluate strategies to ameliorate the long-term adverse effects of COVID-19.

Disclosure statement

The authors declare no conflicts of interest.

Acknowledgments

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