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Post-infection pulmonary sequelae after COVID-19 among patients with lung transplantation

Luke D. Mahan[1] | Isaac Lill[1] | Quinn Halverson[1] | Manish R. Mohanka[1] | Adrian Lawrence[1] | John Joerns[1] | Srinivas Bollineni[1] | Vaidehi Kaza[1] | Ricardo M. La Hoz[2] | Song Zhang[3] | Corey D. Kershaw[1] | Lance S. Terada[1] | Fernando Torres[1] | Amit Banga[1]

[1] Division of Pulmonary and Critical Care Medicine, University of Texas Southwestern Medical Center, University of Texas System, Dallas, Texas, USA

[2] Infectious Disease and Geographic Medicine, University of Texas Southwestern Medical CenterUniversity of Texas System, Dallas, Texas, USA

[3] Department of Population and Data Sciences, University of Texas Southwestern Medical Center, University of Texas System, Dallas, Texas, USA

Correspondence
Amit Banga, Division of Pulmonary & Critical Care Medicine, Lung Transplant Program, UT Southwestern Medical Center, 5939 Harry Hines Blvd. Suite 603, Dallas, TX 75235-8550, USA.
Email: amit.banga@utsouthwestern.edu

The two authors who contributed equally were Mahan and Lill.

Abstract

Background: There is limited data on outcomes among lung transplant (LT) patients who survive Coronavirus disease 2019 (COVID-19).

Methods: Any single or bilateral LT patients who tested positive for SARS-CoV-2 between March 1, 2020, to February 15, 2021 ($n = 54$) and survived the acute illness were included (final $n = 44$). Each patient completed at least 3 months of follow-up (median: 4.5; range 3–12 months) after their index hospitalization for COVID-19. The primary endpoint was a significant loss of lung functions (defined as > 10% decline in forced vital capacity (FVC) or forced expiratory volume in 1 s (FEV_1) on two spirometries, at least 3 weeks apart compared to the pre-infection baseline).

Results: A majority of the COVID-19 survivors had persistent parenchymal opacities ($n = 29$, 65.9%) on post-infection CT chest. Patients had significantly impaired functional status, with the majority reporting residual disabilities (Karnofsky performance scale score of 70% or worse; $n = 32$, 72.7%). A significant loss of lung function was observed among 18 patients (40.9%). Three patients met the criteria for new chronic lung allograft dysfunction (CLAD) following COVID-19 (5.6%), with all three demonstrating restrictive allograft syndrome phenotype. An absolute lymphocyte count $< 0.6 \times 10^3$/dl and ferritin > 150 ng/ml at the time of hospital discharge was independently associated with significant lung function loss.

Conclusions: A significant proportion of COVID-19 survivors suffer persistent allograft injury. Low absolute lymphocyte counts (ALC) and elevated ferritin levels at the conclusion of the hospital course may provide useful prognostic information and form the basis of a customized strategy for ongoing monitoring and management of allograft dysfunction.

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Lung transplant patients who survive COVID-19 suffer significant morbidity with persistent pulmonary opacities, loss of lung functions, and functional deficits. Residual elevation of the inflammatory markers is predictive.

KEYWORDS

allograft dysfunction, CLAD, COVID survivors, predictors, SARS-CoV-2, survival

1 | INTRODUCTION

The early impact of Coronavirus disease 2019 (COVID-19) among patients with lung transplantation (LT), including the significant in-hospital morbidity and mortality, has now been reported by multiple groups across different countries.[1–5] Despite improved hospital survival in more recent studies,[1,3] LT patients with COVID-19 seem to be at an increased risk of severe diseases such as the development of respiratory failure and need for respiratory support strategies that require intensive care unit (ICU) admission. A more severe clinical course consisting of lower respiratory tract involvement with respiratory viral infections (RVI) has been reported to increase the risk of progressive allograft injury among LT patients.[6]

The focus of a large majority of the current work has been the acute illness and its impact on the allograft, which by virtue of being the target of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is at a uniquely high risk of dysfunction compared to patients with other types of solid organ transplantation. However, there is limited data on outcomes among the patients who survive COVID-19.

As a group, RVIs have been associated with post-infection allograft dysfunction among LT patients via activation of alloimmune pathways that increase the risk of chronic lung allograft dysfunction (CLAD).[7–9] Furthermore, previous research has demonstrated that acute illness from SARS-Cov-2 infection is more severe than a respiratory syncytial virus (RSV) in LT patients.[1] Apart from the direct injury to the allograft from the SARS-Cov-2 virus, the secondary damage from the activation of systemic inflammatory pathways, coagulation dysfunction, and immunothrombosis are all somewhat unique to COVID-19.[10,11] Furthermore, COVID-19 has the potential for significant long-term effects even among non-transplant patients.[12] These considerations raise the concerns regarding the long-term implications of COVID-19 among LT patients and its impact on the allograft. Indeed, there are isolated reports of LT patients with COVID-19 experiencing accelerated progression to CLAD after recovering from acute infection.[13,14]

The current work reports the outcomes after COVID-19 among LT patients who survive acute illness, focusing on post-infection spirometry. We sought to determine the frequency of significant loss of lung functions assessed via spirometry among a cohort of COVID-19 survivors. In addition, we elucidated clinical predictors that could facilitate prognostication and permit consideration of customized management strategies during the acute infection with SARS-CoV-2.

2 | METHODS

The current study was a single-center chart review study approved by the UT Southwestern Medical Center Institutional Review Board (#STU-2020-1400). Any patient with a history of single or bilateral LT who tested positive for SARS-CoV-2 on a nasopharyngeal swab between March 1, 2020, to February 15, 2021, and survived the acute illness (referred to as 'COVID-19 survivors') was eligible for inclusion. The swabs were collected from symptomatic patients and tested for the SARS-CoV-2 virus using the quantitative polymerase chain reaction assay. This assay targets the nucleocapsid and RdRp genes of the novel Coronavirus using the Abbott Alinity m SARS-CoV-2 assay.

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. The cornerstone of the management included the early institution of a multimodality pharmacological strategy consisting of antiviral agent, passive immune augmentation, and the attenuation of the hyper-inflammatory phase of the SARS-CoV-2 infection and post-viral alloimmune responses. The details regarding indications for hospitalization as well as the multimodality pharmacotherapeutic strategies have been described earlier.[1]

The hospitalized patients were instructed to resume their home spirometry monitoring protocol (twice daily using a micro-spirometer) after discharge. Outpatient follow-up consisted of a clinic visit 2 weeks after the discharge or recovery from acute illness (defined as 28 days from the symptom onset) with subsequent visits at the discretion of the managing physician. All patients underwent testing with office spirometry and chest radiograph during their clinic visit. Late in 2020, protocols were instituted to obtain post-discharge CT chest at 4–6 weeks or beyond the diagnosis of COVID-19 during their clinic visit. Each patient completed at least 3 months of follow-up after their index hospitalization for COVID-19 or the acute illness.

Patient variables were recorded directly from the electronic medical records and consisted of patient demographics (age, gender, and race), transplant indication, pre-transplant comorbidities, immunosuppressive regimen at the time of infection, and presenting symptoms. Pre-infection baseline spirometry, defined as an average of two measurements of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), at least 3 weeks apart, during the 3–6 months preceding the infection, laboratory abnormalities including inflammatory markers, and radiological findings were also reviewed. Complications such as new or worsening respiratory failure, admission to the ICU, and need for ventilator support (non-invasive or invasive), were recorded. Finally, we recorded the length of the hospital stay, post-infection findings on CT chest, functional status, and spirometry (FVC and FEV_1). We also queried for a sustained and significant loss of FVC or FEV_1 (>10% on two spirometries, at least 3 weeks apart) as compared to their pre-infection baseline during the follow-up period as well as the type of ventilatory defect among patients with a loss of lung functions.

All spirometric testing was conducted in the lung transplant clinic using the Vyntus Spiro systems and Vyaire's SentrySuite software platform. All spirometry analyses met the American Thoracic Society standards.[15]

Each patient chart was independently reviewed by a lung transplant nurse practitioner (Luke D. Mahan) and a transplant pulmonologist (Amit Banga) to evaluate the lung function data and determine the pre, and post-infection diagnosis of CLAD based upon the International Society for Heart & Lung Transplantation criteria.[16]

2.1 | Statistical analysis

Data were described as median with range, mean with standard deviation, or proportions as appropriate. The primary endpoint for the study was a post-infection significant loss of lung functions (FVC or FEV_1). We compared the characteristics and outcomes among patients with and without spirometry decline. The univariate comparison was made using the Chi-squared test for categorical and Mann-Whitney *U* test for quantitative variables. Receiver operator characteristics curves were constructed to assess the performance of predictor variables for loss of lung function and to identify the best cut-offs. Variables were selected as potential covariates for entering into a multivariate logistic regression model on the basis of them achieving significance at $p < 0.1$ on univariate analysis. In addition, we selected age, gender, transplant indication, pre-infection CLAD, and respiratory failure as potential confounder variables and entered them in the multivariate model to identify variables independently associated with post-infection loss of lung functions.

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.)

3 | RESULTS

During the study period, 54 patients were diagnosed with COVID-19, the majority of which were hospitalized ($n = 50$, 92.6%). Among the four patients managed as outpatients, three were approved for bamlanivimab infusion (only available for outpatients) and did not need hospitalization. The remaining patient opted not to be admitted. Overall, 45 patients (including the four managed as outpatients) survived the acute illness or its complications (overall survival: 83.3%). One of the discharged COVID-19 survivors died of disseminated malignancy and did not return for post-discharge clinic follow-up. The remaining 44 patients were included in the final analysis.

The mean age of COVID-19 survivors was 58 ± 12 years (range 20-73 years), where the majority were Caucasians ($n = 27$, 61.4%) and males ($n = 33$ 75%) with a mean body mass index of 28 ± 5.5 Kg/m^2. Restrictive lung disease was the most common transplant indication ($n = 31$, 70.5%), and a majority of the patients had received a bilateral LT ($n = 34$, 77.3%). Median time from LT to the diagnosis of COVID-19 was 50 months (range 5–139 months), while a significant proportion of the COVID-19 survivors had established CLAD before the infection ($n = 12$, 27.3%). Patients had completed a median follow-up of 4.5 months (range 3–12 months) from hospital discharge or the acute illness. All included patients were alive at the time of this report.

3.1 | Outcomes among COVID-19 survivors

During the course of acute illness, parenchymal involvement was evident on chest radiographs among a majority of the study group ($n = 27$, 61.4%), while it was nearly ubiquitous among the patients where a CT chest was available (34/39, 87.2%). At the time of the most recent clinic assessment, a majority of the COVID-19 survivors had persistent parenchymal opacities related to COVID-19 on post-infection chest radiographs (21/27, Figure 1A–C) and CT chest, where available (22/28, Figure 1D–F). The overall burden of persistent pulmonary opacities in the current cohort was 65.9% (29/44). The most common types of opacities consisted of persistent ground glass or consolidative changes with evidence of organization, by way of varying degrees of reticular markings, in the areas of the ground glass opacities at the time of acute infection (20/22, 91%, Figure 1F). Twelve of the 22 scans had parenchymal bands, and eight showed persistent pulmonary nodules. Most of the CT chest (17/22) had multiple abnormalities on the follow-up CT chest.

Patients had significantly impaired functional status, with the majority reporting residual disabilities (Karnofsky performance scale (KPS) score of 70% or worse; $n = 32$, 72.7%). However, severe disability (KPS score ≤40%) was infrequent ($n = 7$, 15.9%). A persistent and significant loss of FVC or FEV_1 (>10% from pre-COVID-19 baseline) was observed among 18 patients (40.9%), and a large majority of these patients had a restrictive or mixed ventilatory defect on spirometry ($n = 15$, 83.3%). The loss of lung functions was not associated with the severity of functional impairment at follow-up (median KPS 70%, range 20%–80% vs. 70%, range 30%–80%, $p = 0.83$). Three patients met the criteria for CLAD (incidence of new CLAD after COVID-19 infection: 5.6%), with all of them demonstrating restrictive allograft syndrome (RAS) phenotype.

3.2 | Predictors of loss of lung functions

The baseline characteristics of the patients with and without significant loss in FVC or FEV_1 after COVID-19 are compared in Table 1. Although none of the comparisons achieved statistical significance, patients with restrictive lung disease appeared to be at a higher risk of significant loss in lung functions, while those with obstructive lung disease were at lower risk. In addition, although statistically not significant, patients with a lower reserve, as reflected by the lower median pre-infection FVC and FEV_1, may be at a higher risk of post-COVID-19 lung function loss. They also appeared to have a more severe illness at presentation as reflected by a higher incidence of lower respiratory tract symptoms and spirometry decline at presentation, opacities on chest radiographs, and need for hospitalization.

The laboratory variables during the course of acute illness are compared between the two groups in Table 1. Both groups appeared to have similar laboratory profiles at the onset of illness. However, persistently lower absolute lymphocyte count (ALC) and higher ferritin levels at hospital discharge were associated with post-discharge lung function loss. On the receiver operator characteristics analysis, an ALC < 0.6 $X10^3$/dl (Figure 2A, area under the curve (AUC): 0.736, $p = 0.015$; sensitivity: 78.3% and specificity: 73.3%) and ferritin > 150 ng/mL (Figure 2B, AUC: 0.701, $p = 0.038$; sensitivity: 80%

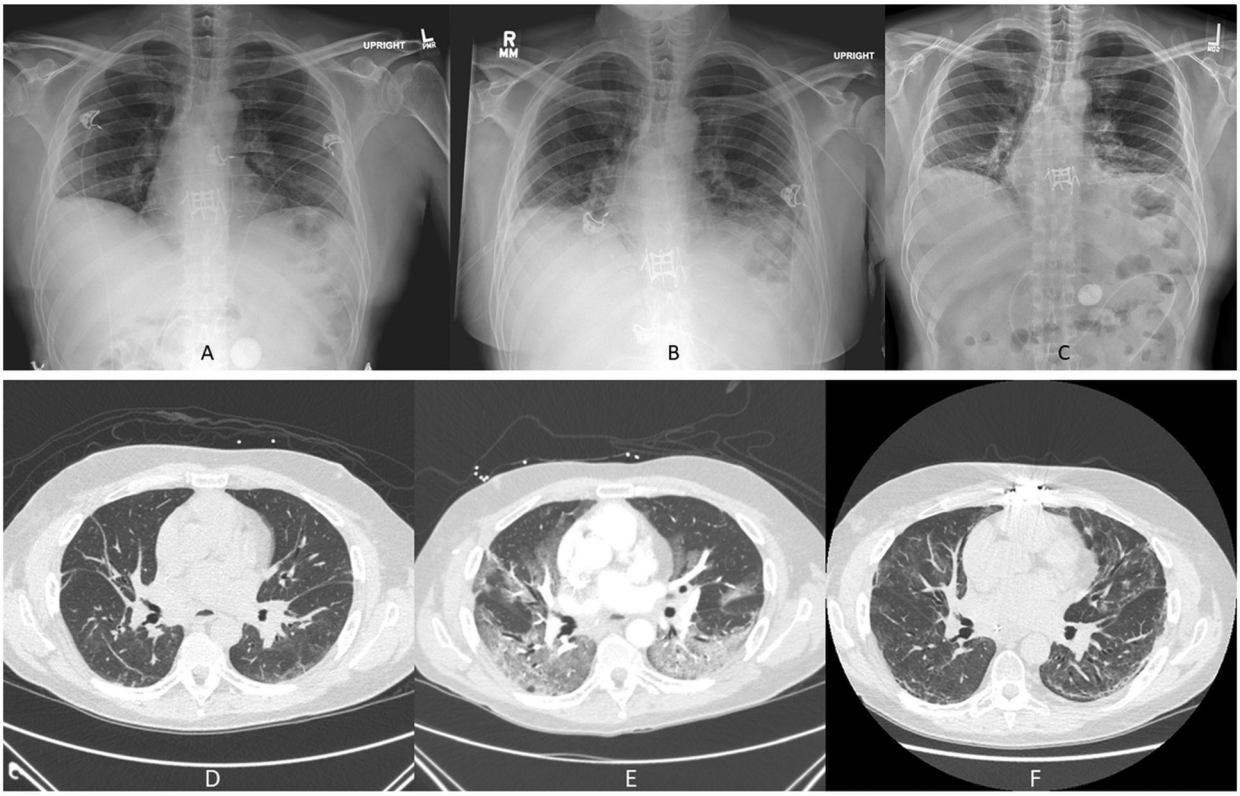

FIGURE 1 (A–F) Serial chest radiographs of a lung transplant (LT) patient with COVID-19. This is a 52-year-old male patient with scleroderma who underwent bilateral LT in September 2019. He presented with fevers and tested positive for SARS-CoV-2 on a nasopharyngeal swab. He developed acute hypoxic respiratory failure during the hospital stay but did not need intensive care unit (ICU) admission. He was treated with remdesivir (10 doses), two units of convalescent plasma, and pulse dose corticosteroids (10 mg/Kg IV daily for 3 days). (A) Baseline chest radiograph (1 month before COVID-19). (B) Chest radiograph during acute illness showing new bibasilar hazy and reticular opacities. (C) Chest radiograph 6 months after COVID-19 showing persistence of bibasilar reticular opacities. (D) Baseline CT chest of the same patient (1 month before COVID-19) showed predominant findings of post-surgical changes indicated by scattered parenchymal bands. (E) CT chest during the acute illness: There is interval development of diffuse ground-glass opacities with consolidative changes involving the lower lobes with similar but less severe involvement of the right middle lobe and lingula. (F) CT Chest 2 months after COVID-19: There are much improved but persistent ground glass and peri-broncho-vascular consolidative opacities. There is a development of subpleural scarring predominantly involving the left lower lobe. There is lower lobe predominant bilateral diffuse bronchiectasis

and specificity: 65.2%) at the time of discharge were identified as the best cut-off for predicting a significant loss of lung functions.

While the pharmacotherapeutic strategies were similar among the two groups (Table 2), patients with acute chronic respiratory failure appeared more likely to suffer loss in lung functions ($p > 0.05$). Although the need for ICU admission during the acute illness predicted subsequent lung function loss, the need for readmission and cumulative length of hospital stay were similar between the two groups.

On multivariate logistic regression analysis, ALC $< < 0.6$ X10^3/dl (adjusted odds ratio (OR): 100.7, 1.84–5515.6; $p = 0.024$) and ferritin > 150 ng/mL (adjusted OR: 59.9, 1.5–2396.5; $p = 0.03$) at hospital discharge were independently associated with significant lung function loss while obstructive lung disease as the transplant indication appeared to be protective (adjusted OR: 0.532, 0.28–1.0; $p = 0.05$).

4 | DISCUSSION

The current study reports the outcomes among a cohort of lung transplant patients who survived COVID-19. We focused on assessing the impact of COVID-19 on lung functions beyond acute illness. We found that a high proportion of COVID-19 survivors are left with structural abnormalities on their allografts and impairment in pulmonary physiology on spirometry. Furthermore, we identified two laboratory variables, ALC, and ferritin, during the index hospitalization that emerged as independent predictors of significant loss of lung functions.

A small but significant proportion of patients met the criteria for new CLAD after COVID-19. All these patients were classified as RAS phenotype based on the restrictive pulmonary physiology and typical radiological changes. However, these radiological abnormalities were essentially indistinguishable from post-COVID opacities among other patients in the study group who did not meet the physiologic criteria.

TABLE 1 Comparative analysis of baseline characteristics and laboratory abnormalities during the acute illness among lung transplant patients with and without significant spirometry decline after COVID-19

	Post-infection spirometry decline >10%			
Variable	**Yes ($n = 18$)**	**No ($n = 26$)**	**Odds ratio (95% CI)**	***p*-value**
Age	58 (20–70)	60.5 (21–72)		.33
BMI at diagnosis (Kg/m^2)	26.4 (17–40)	28.1 (20–39)		.4
Male gender	72.2%	76.9%	0.78 (0.2–3.1)	.74
Caucasian	55.6%	65.4%	0.66 (0.19–2.27)	.54
Transplant Indication (%)				.13
Restrictive	83.3	61.5		
Obstructive	5.6	23.1		
Suppurative	11.1	3.8		
Vascular		11.5		
Bilateral Transplant	88.9%	69.2%	3.56 (0.66–19.3)	.16
Time since transplant (months)	48 (10–100)	39 (5–139)		.26
Baseline FEV_1 before the infection (L)	2.01 (0.99–4.32)	2.38 (0.49–4.7)		.59
Baseline FVC before the infection (L)	2.79 (2.06–4.53)	3.03 (1.24–5.21)		.61
Diabetes mellitus	33.3%	57.7%	0.37 (0.11–1.28)	.14
Co-morbid renal dysfunction[†]	44.4%	46.2%	0.93 (0.28–3.1)	1.0
Established pre-infection CLAD	27.8%	26.9%	1.04 (0.27–4.02)	1.0
Duration of symptoms at diagnosis (days)	2.5 (0–10)	3 (1–7)		.93
Lower respiratory tract symptoms at presentation	83.3%	61.5%	3.13 (0.72–13.6)	.18
Spirometry (FEV_1 or FVC) decline of >10% at presentation	42.9% (n = 14)	31.6% ($n = 20$)	1.63 (0.39–6.82)	.72
Opacities on chest radiograph at presentation	77.8%	46.2%	4.08 (1.06–15.8)	.06
Opacities consistent with COVID-19 on CT chest	93.3% ($n = 15$)	83.3% ($n = 24$)	2.8 (0.28–27.8)	.63
Hospitalization	100%	84.6%		.13
Lymphocyte count ($\times 10^3$/dL)				
At diagnosis	1.42 (0.76–2.94)	1.22 (0.4–2.71)		.41
Lowest during admission	0.25 (0–0.78)	0.28 (0–0.94)[*]		.273
At hospital discharge	0.41 (0.23–2.45)	0.89 (0–2.24)[*]		.014
Lymphocyte counts < 0.6 $\times 10^3$/dl at discharge from hospital	72.2%	22.7%[*]	8.84 (2.1–37.1)	.003
Ferritin (ng/ml)				
At diagnosis	200 (15–1336)	200 (36–1637)		.67
Highest during admission	620 (64–3373)	212 (40–3614)[*]		.06
At hospital discharge	349 (56–2232)	113 (22–2627)[*]		.04
Ferritin levels > 150 ng/ml/L at discharge from hospital	72.2%	31.8%[*]	5.57 (1.42–21.9)	.02
Lymphocyte counts < 0.6				.001
$\times 10^3$/dl and Ferritin levels				
>150 ng/ml at discharge from				
hospital				
None	None	54.5%[*]		
Either	50%	40.9%[*]		
Both	50%	4.5%[*]		

(Continues)

TABLE 1 (Continued)

Variable	Post-infection spirometry decline >10%		Odds ratio (95% CI)	*p*-value
	Yes (*n* = 18)	No (*n* = 26)		
D-dimer (mcg/ml)				
At diagnosis	0.43 (0.25–1.29)	0.92 (0.17–32.6)		.17
Highest during admission	0.97 (0.17–32.8)	0.66 (0.09–6.0)*		.63
At hospital discharge	0.52 (0.17–6.28)	0.6 (0.17–5.77)*		.77
C-reactive protein (mg/L)				
At diagnosis	5.0 (0.4–59.4)	5.25 (0.03–37.4)		.95
Highest during admission	38.9 (6.1–256.4)	35 (2.2–116.6)*		.6
At hospital discharge	3.6 (0.4–23.4)	4.2 (0.4–17.9)*		.46
Lactate dehydrogenase (U/L)				
At diagnosis	216 (145–341)	200 (124–376)		.87
Highest during admission	301 (350–789)	290 (199–600)*		.87
At hospital discharge	269(151–556)	239 (156–600)*		.34

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
†Defined as CKD-3 or higher.
*n = 22.

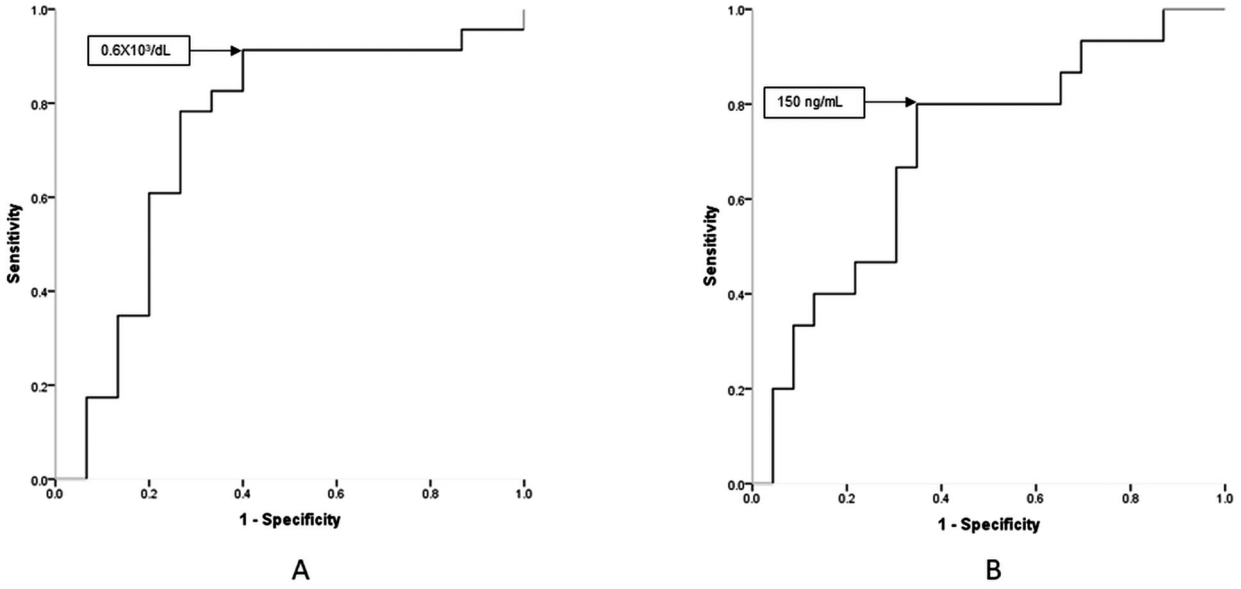

FIGURE 2 (A–B) Receiver operator characteristic curves to assess the predictive capability of variables for significant lung function loss after COVID-19. (A) Absolute lymphocyte counts (ALC) at discharge from hospital. The area under the curve (AUC) for ALC was 73.6%, (95% CI: 55.6%–91.6%), $p = .015$ with 0.6 × 103 /dl as the best cut-off. (B) Serum ferritin at the time of hospital discharge. The AUC for ferritin was 70.1% (95% CI: 53%–87.3%), $p = .038$ with 150 ng/ml as the best cut-off

It remains to be seen if the natural history of post-COVID CLAD, especially the RAS phenotype, will mirror the typically ominous outlook of the usual RAS. It is indeed possible that some of these opacities may resolve with time, and such patients may no longer meet the RAS criteria.

We defined the significant loss of lung functions as at least a 10% or more decline in either FVC or FEV_1 on post-infection spirometry on two or more occasions. This variable has been found to be a useful predictor of adverse outcomes after RVI among LT patients, although it has not been studied among patients with COVID-19.[17,18] In a large cohort of LT patients with RSV infection, an early decline in $FEV_1 > 10\%$ was noted among 13% of the patients and was an independent predictor of post-RSV mortality.[18] Similarly, our group found that more than a third of the LT patients suffered > 10% decline in FEV_1 or FVC during the 6 months after RSV infection and, along with pre-infection CLAD, was an independent predictor of mortality at one year after the RSV infection.

TABLE 2 Comparison of management strategies and clinical course among lung transplant patients with and without significant spirometry decline after COVID-19

Variable	Post-infection spirometry decline >10%		Odds ratio (95% CI)	*p*-value
	Yes (n = 18)	No (n = 26)		
Monoclonal antibody[†]	22.2%	7.7%	3.42 (0.55–21.2)	.2
Remdesivir	83.3%	84.6%	0.91 (0.18–4.66)	1.0
Time from symptom onset to Remdesivir initiation (days)	5 (1–20)	3 (1–8)		.15
Convalescent plasma	61.1%	80.8%	0.37 (0.09–1.46)	.18
Time from symptom onset to Convalescent plasma (days)	4 (1–20)	4 (1–8)		.75
Pulse corticosteroids	61.1%	57.7%	1.15 (0.34–3.93)	1.0
Acute or acute on chronic respiratory failure	50%	26.9%	2.71 (0.77–9.63)	.2
Need of ICU admission	27.8%	3.8%	9.62 (1.01–91.2)	.034
Need of ventilator support	16.7%	3.8%	5.0 (0.48–52.53)	.29
Need for readmission	44.4%	27.3%*	2.13 (0.57–8.0)	.33
Cumulative length of hospital stay (days)[∞]	10 (2–49)	10 (4–12)		.62
Post-COVID-19 pulmonary opacities[∞]	77.8%	57.7%	4.76 (0.51–44.4)	.2
Karnofsky score at the last follow up visit				.49
≤40%	11.1%	19.2%		
50–70%	66.7%	50%		
≥80%	22.2%	30.8%		

[†]Includes Bamlanivimab and Casirivimab-Imdevimab combination.
[∞]Combined length of stay from the primary admission and readmission.

Compared to other RVI, COVID-19 survivors seem more likely to suffer a sustained decline in FEV_1 or FVC. Our analysis indicates the significantly worse morbidity after COVID-19 among LT patients, especially considering that we limited our analysis to COVID-19 survivors only. Alternatively, the proportion of patients experiencing the composite endpoint of significant lung function loss or death from COVID-19 exceeded 50% in the current cohort (28/54). Furthermore, the median follow-up in the current analysis was shorter (4.5 months) than the earlier studies among RSV patients, which may have underestimated the true morbidity burden, as additional patients could suffer a delayed loss in lung functions beyond the study period. Conversely, one can not discount the possibility that, among some patients, the lung function loss may be driven by reversible factors such as debility (although we did not find an association of KPS with lung functions) and such patients may recover some of their lost lung functions on longer follow up.

The post-acute illness outcomes in the current report appear worse than the only other study evaluating post-discharge outcomes among COVID-19 patients, where an FEV1 decline > 10% was noted among five out of the 21 patients.[19] However, the differences are possibly linked to the variability in study design, inclusion criteria, and definition of endpoints. It appears that COVID-19 patients in the current study ($n = 54$) had more risk factors for the severe disease at presentation, as a higher proportion of patients had pertinent comorbidities such as diabetes (48.1%) and stage 3 or worse chronic kidney disease (46.3%). Additionally, a third of the patients had established CLAD at the time of the diagnosis of COVID-19. Finally, the follow-up period of the study by Permpalung et al.[19] was limited to 90 days which may have underestimated the post-infection loss in lung functions.

Predictors of lung function loss after COVID-19 among LT patients have not been reported before. Although the patients with significant lung function loss tended to have more advanced disease at presentation and a more complicated hospital course, few variables achieved statistical significance. Among the laboratory abnormalities, ALC and ferritin levels at the time of hospital discharge emerged as independent predictors of lung function loss. The severity of laboratory abnormalities, indicative of the extent of the inflammatory milieu, have been associated with worse outcomes among non-transplant patients,[20–23] although we did not find them to predict hospital outcomes among LT patients.[1] Similarly, none of the laboratory variables at presentation or during the hospital course were associated with the subsequent lung function loss in the current analysis. Instead, elevated ferritin and suppressed ALC at hospital discharge appeared to predict significant lung function loss. It is noteworthy that none of the 12 patients with ALC > 0.6×10^3/dl and ferritin < 150 ng/ml at the time of hospital discharge suffered a significant loss in lung functions. This suggests that the severity of inflammatory response at the time of diagnosis or its peak during the course of acute illness may not be as consequential as the persistence of the inflammatory milieu among LT patients.

The mechanisms for low ALC during COVID-19 are not well understood, although it is believed to be the effect of the cytokine storm from the active infection, mediated via the pro-inflammatory cytokines.[24]

The association of low ALC with worse post-infection outcomes incriminates the acute infection, instead of the activation of alloimmune pathways, as the likely culprit for subsequent allograft dysfunction. The role of ferritin as a predictor of outcomes among patients with COVID-19 remains unclear. Studies from China found that ferritin levels were associated with disease severity, although it is unclear if it is a by-product or a mediator of the cytokine storm.[23] Hyperferritinemia in COVID-19 has been likened to secondary hemophagocytic lymphohistiocytosis and is a key mediator of pulmonary fibrosis that can follow severe COVID-19.[25] Intriguingly, the extent of ferritin elevation has been found to predict the severity of lung involvement assessed via CT chest among patients with COVID-19.[26] It is indeed possible that persistent hyperferritinemia predisposes patients to ongoing allograft injury and subsequent loss of lung functions.

While the association of laboratory abnormalities with lung function loss needs to be confirmed in larger studies, they do appear biologically plausible. The prompt initiation of anti-inflammatory therapies could blunt the effects of cytokine-mediated allograft injury during the peak of COVID-19, while ongoing low-grade smoldering inflammation may predispose patients to the subsequent loss of lung functions. It may, therefore, be prudent to continue monitoring inflammatory markers and consider an extended course of anti-inflammatory agents, such as a long taper of oral corticosteroids, among patients with persistent laboratory abnormalities.

The current analysis has some limitations. Our analysis did not differentiate among patients who may be suffering ongoing lung function decline before COVID-19. The post-infection lung function loss assessment can be confounded by such patients where the lung function decline may have occurred irrespective of the infection. While we cannot completely exclude such a possibility in the occasional patient, using the most recent spirometries to determine the pre-infection baseline while assessing post-infection lung function loss reduces the likelihood of falsely ascribing the lung function loss to COVID-19. Despite being the largest study to date reporting post-acute illness outcomes, the study was not powered to determine additional statistically significant associations with the endpoint. Additionally, the model could not be fitted with all potential confounders, and fully adjusted associations must await studies that include a larger sample size. Regardless, we did have additional clinically relevant variables in the multivariate model to adjust the associations for these variables apart from those significant on univariate analysis (at p-value $< .1$). Although we identified independent predictors of lung function loss among COVID-19 survivors and the associations do appear biologically plausible, causality cannot be determined and must await mechanistic studies in the future.

It is concluded that a significant proportion of COVID-19 survivors suffer persistent allograft injury as reflected by the parenchymal opacities and loss of lung functions on spirometry. While post-viral activation of alloimmune pathways can contribute, the allograft injury from COVID-19 may be driven by the smoldering inflammation linked to the acute infection. A persistently low ALC and elevated ferritin at the conclusion of the hospital course may provide useful prognostic information and form the basis of a customized strategy for ongoing monitoring and management of allograft dysfunction.

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None.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Study design: Amit Banga; Data collection and management: Luke D. Mahan, Isaac Lill, Quinn Halverson, and Amit Banga; Data analysis: Amit Banga; Preparation of the manuscript: Luke D. Mahan, Manish R. Mohanka, John Joerns, Adrian Lawrence, Vaidehi Kaza, Srinivas Bollineni, Ricardo M. La Hoz, Song Zhang, Lance S. Terada, Corey D. Kershaw, Fernando Torres, and Amit Banga.

ORCID

Luke D. Mahan https://orcid.org/0000-0002-7023-326X
Isaac Lill https://orcid.org/0000-0001-9096-6084
Vaidehi Kaza https://orcid.org/0000-0003-3578-6077
Ricardo M. La Hoz https://orcid.org/0000-0002-1560-3192
Corey D. Kershaw https://orcid.org/0000-0002-9696-1994
Amit Banga https://orcid.org/0000-0002-6932-1537

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