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Predictors and outcomes of respiratory failure among lung transplant patients with COVID-19

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Abstract

Background: There is limited data on the predictors and outcomes of new or worsening respiratory failure among lung transplant (LT) patients with Coronavirus disease 2019 (COVID-19).

Methods: We included all the LT patients diagnosed with COVID-19 during a 1-year period (March 2020 to February 2021; $n = 54$; median age: 60, 20–73 years; M:F 37:17). Development of new or worsening respiratory failure (ARF) was the primary outcome variable.

Results: The overall incidence of ARF was 48.1% ($n = 26$). More than 20% of patients ($n = 11$) needed intubation and mechanical ventilation. Body mass index > 25 Kg/m^2 (adjusted OR: 5.7, .99–32.93; $P = .05$) and peak D-dimer levels > .95 mcg/ml (adjusted OR: 24.99, 1.77–353.8; $P = .017$) were independently associated with ARF while anticoagulation use prior to COVID-19 was protective (adjusted OR: .024, .001–.55; $P = .02$). Majority patients survived the acute illness (85.2%). Pre-infection chronic lung allograft dysfunction (CLAD) was an independent predictor of mortality (adjusted HR: 5.03, 1.14–22.25; $P = .033$).

Conclusions: COVID-19 is associated with significant morbidity and mortality among LT patients. Patients on chronic anticoagulation seem to enjoy favorable outcomes, while higher BMI and peak D-dimer levels are associated with development of ARF. Pre-infection CLAD is associated with an increased risk of death from COVID-19.

KEYWORDS
allograft dysfunction, anticoagulants, coagulation, D-dimer, SARS-CoV-2, survival

1 | INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused worldwide suffering with millions of deaths.[1] While the virus is highly infectious, even before the onset of symptoms,[2] it mostly leads to mild illness among young and healthy individuals.[3] However, the clinical manifestations of COVID-19 are much more significant for older patients and those with significant comorbidities.[4]

The clinical effects of the SARS-CoV-2 infection encompass the direct effects from viral proliferation followed by a more ominous systemic hyper-inflammation with varying degrees of severity.[5] The

overall risk of respiratory failure is estimated to be between 5% and 15%, with a minority of patients progressing to acute respiratory distress syndrome (ARDS), multiorgan failure (MOF), and death.[6,7] Among patients with solid organ transplantation (SOT), the consequences of COVID-19 have generally been worse.[7,8] While a weakened immune system may increase the risk of acquiring the infection and developing lower respiratory tract (LRT) involvement, it has been speculated that maintenance immunosuppression may protect against systemic hyper-inflammation.[9] Furthermore, the implications of COVID-19 may be variable among patients with different SOT. Specifically, patients with lung transplantation (LT) are likely more vulnerable by virtue of the allograft itself being the target of the SARS-CoV-2.[8] Apart from the usual effects related to COVID-19, LT patients may also be at risk for post-infection allograft dysfunction from the activation of alloimmune responses.[10] However, there is limited data regarding the spectrum of severity of COVID-19 among LT patients. The burden of severe disease, as reflected by the development of new or worsening respiratory failure (ARF) and impact on outcomes, is not well described.

The current study aims to address some of the gaps in the knowledge among LT patients with COVID-19. We sought to determine the frequency of severe disease as reflected by the development of ARF and elucidate the variables independently associated with ARF. Finally, we report post-acute illness outcomes and determine the predictors of post-COVID survival.

An analysis of a sub-group (*n* = 25) of the patients included in the current study has been analyzed and reported previously.[11] The current study's larger sample size and more robust statistical analysis aims to expand on the finding from the previous analysis and report independent predictors of outcomes.

2 | METHODS

The current study was a single-center retrospective chart review study approved by the UT Southwestern Medical Center Institutional Review Board (# STU-2020-1400). All patients with a history of single or bilateral LT who tested positive for SARS-CoV-2 on a nasopharyngeal swab were included. The swabs were collected for symptomatic patients between March 1, 2020, and February 15, 2021, 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. This test was validated by the UT Southwestern Medical Center Molecular Diagnostics Lab, and the limit of detection of the assay was 100 copies/ml.

The protocol for testing for SARS-CoV-2 was preformulated. 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. Additionally, LT patients were tested according to the institutional screening protocols before admission to the non-COVID units or before any procedure during the study period. None of these screening tests were posi-

tive, and no patient in the current series was diagnosed based on a pre-procedure or pre-admission screening test.

Patients with respiratory symptoms were classified as having upper respiratory tract (URT) involvement when the symptoms were limited to rhinitis, cough, or pharyngitis. Those classified with LRT manifestations could present with productive cough, wheezing, shortness of breath, a decline in spirometry, or opacities on a chest x-ray or computed tomography. Acute or new respiratory failure was defined as peripheral oxygen saturations < 90%, resting PaO_2 < 55 mm Hg on room air, or $PaCO_2$ > 45 mm Hg. An increase in the home oxygen requirement or worsening of PaCO2 from baseline hypercapnia signified acute on chronic or worsening respiratory failure.

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.[11] The hallmark of the management protocol consisted of the early institution of a multimodality pharmacological strategy consisting of the following agents-

1. Antiviral agent
2. Immune augmentation
3. Corticosteroids to attenuate the post-viral alloimmune responses and hyper-inflammatory phase of the SARS-CoV-2 infection
4. Screening for bacterial super-infection and prophylactic broad-spectrum antibiotics while awaiting the results

Patients did not undergo bronchoscopy routinely during the period of active infection. Screening for other infections was done using non-bronchoscopic sampling techniques such as tracheal aspirate, mini-bronchoalveolar lavage (BAL), and sputum and serum markers as applicable.

Patient variables were recorded directly from the electronic medical records and consisted of patient demographics (age, gender, & race), transplant indication, pre-transplant comorbidities, immunosuppressive regimen at the time of infection, and presenting symptoms. Pre-infection spirometry, laboratory abnormalities, including inflammatory markers and radiological findings, were also reviewed. Complications such as new or worsening respiratory failure, admission to the intensive care unit (ICU), ventilator support (non-invasive or invasive), and rescue measures for refractory hypoxemia were recorded. Finally, we collected the length of the hospital stay and survival.

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.[12] Discrepancies in the adjudicated timing and the determination of CLAD were reconciled.

2.1 | Statistical analysis

Data were described as median with range and proportions as appropriate. The primary endpoint for the study was the development of
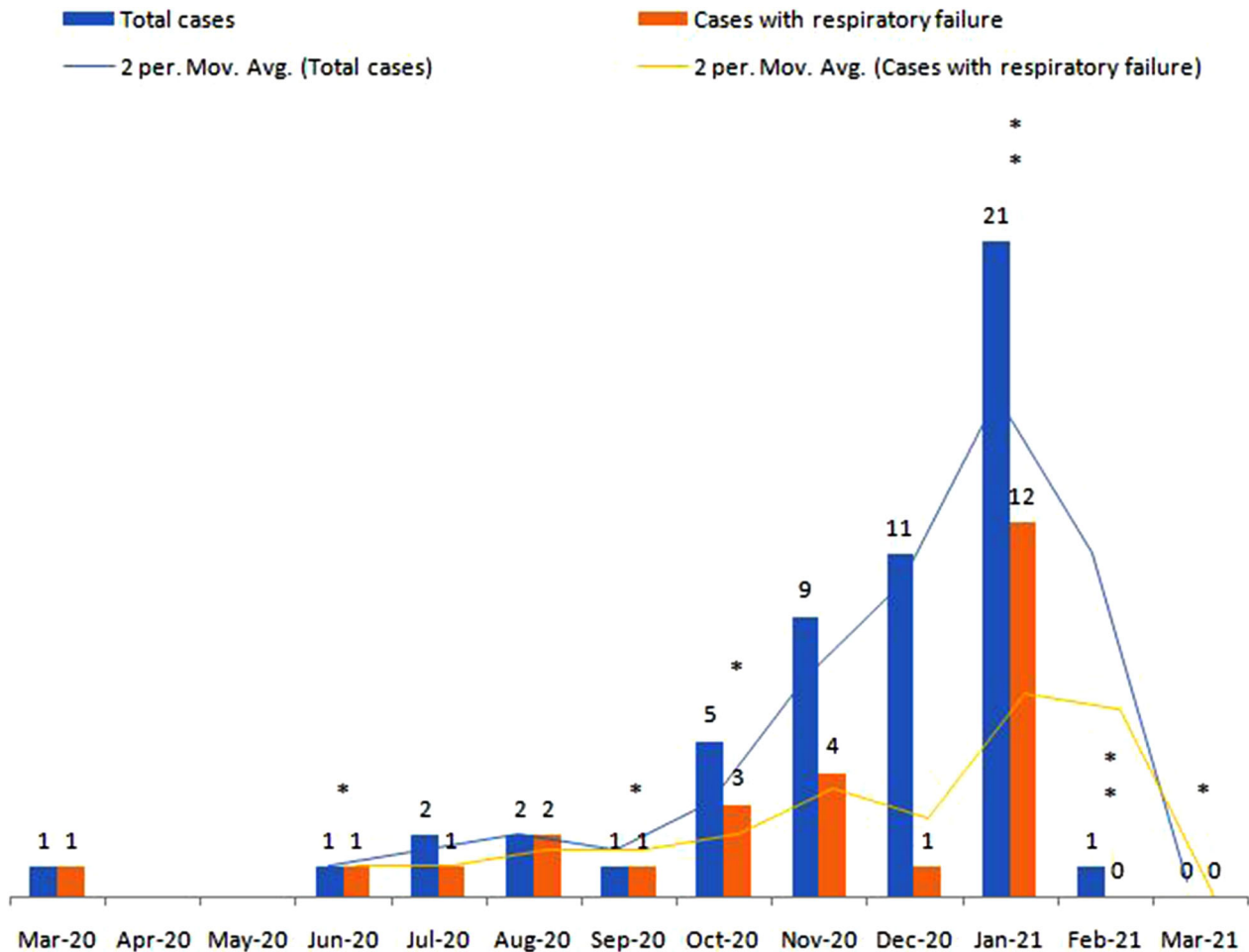
FIGURE 1 Bar diagram showing the monthly incidence of COVID-19 among LT patients and those with new or worsening respiratory failure at the UT Southwestern Medical Center between March 2020 and February 2021. The blue and orange lines demonstrate the two-month moving average for the cases, while the star (*) represents the deaths during the course of the pandemic

either acute or acute on chronic respiratory failure anytime during the course of illness. We compared the characteristics and outcomes among patients with and without respiratory failure. Univariate comparison was made using the Chi-square test for categorical and Mann-Whitney U test for quantitative variables. Variables significant at $P < .1$ on univariate analysis were entered as covariates in a multivariate logistic regression model to identify variables independently associated with new or worsening respiratory failure. Receiver operator characteristics (ROC) curve were constructed to assess the performance of variables in predicting ARF and to determine the best cut-off values. Finally, we analyzed the dataset with post-COVID-19 survival as the dependent variable. Analysis for survival started at the time of diagnosis of COVID-19 and followed for at least 4 weeks from the onset of acute illness. Cox regression analysis was conducted to determine independent predictors of post-COVID-19 survival.

Statistical significance was considered at $P < .05$ (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, USA: IBM Corp.)

3 | RESULTS

During the study period, 54 patients with a history of LT were diagnosed with COVID-19 (median age with range: 60, 20–73 years; M:F 37:17; Caucasian race: 64.8%; BMI: 27.6, 17–40 Kg/m^2). The most common transplant indication among the study group was restrictive lung diseases ($n = 41$, 76%), and the majority had a history of bilateral LT ($n = 41$). Two patients had a history of lung-liver transplantation, and one patient had undergone triple organ transplantation (heart-lung-kidney). Median time since LT was 48 months (range: < 1 to139 months) and a large majority of patients were beyond the first year of LT ($n = 47$; 87%). Almost all infections were community-acquired ($n = 53$).

The monthly incidence of positive cases and the number of patients with ARF is presented in Figure 1. While the first patient with COVID-19 was diagnosed in March, a majority of infections occurred between November 2020 and January 2021 ($n = 41$), with January accounting for the highest number of infections ($n = 21$, 38.9%). The proportion of patients with ARF was higher during the early months of the
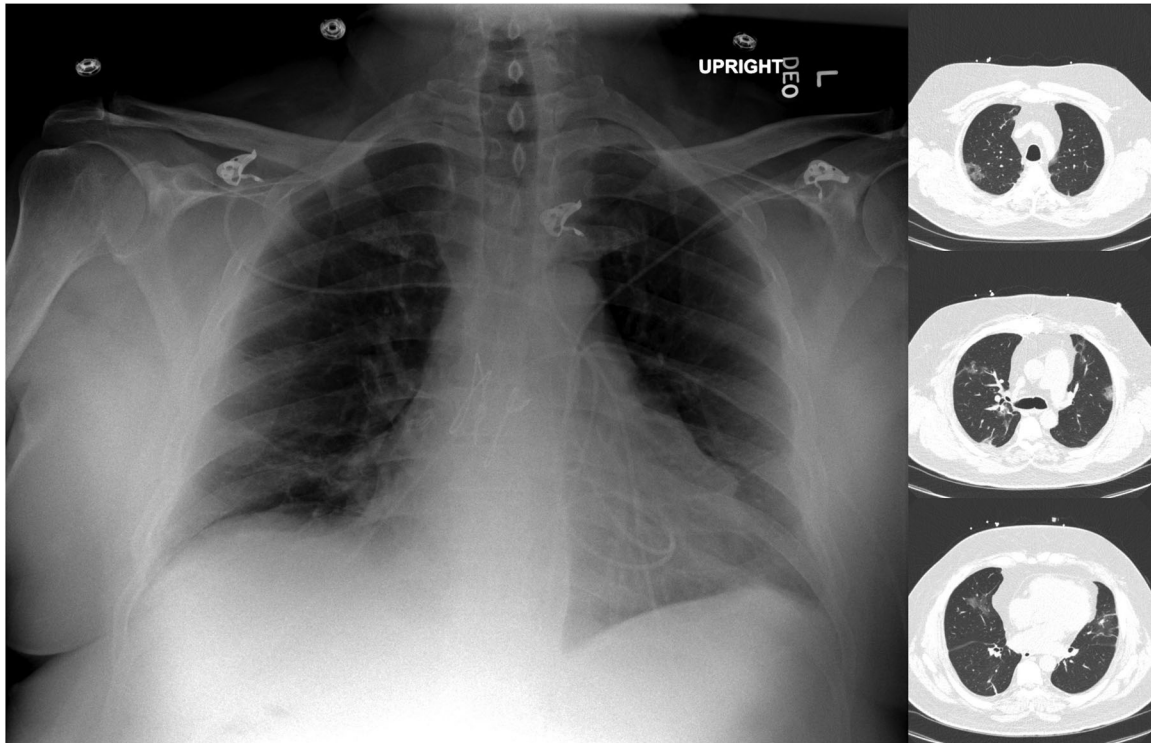
FIGURE 2 65/M patient with a history of bilateral LT who presented with cough and shortness of breath after contact with a family member with COVID-19. He was confirmed to be positive for the SARS-CoV-2 virus on the nasopharyngeal swab. His chest radiograph was unremarkable, but screening CT chest revealed bilateral nodular ground-glass opacities. He was treated per the standard protocol but progressed to develop acute respiratory failure. However, he did not need ICU admission and was weaned off oxygen and discharged home on room air

pandemic (March to October) and stabilized around 50% after that. Notably, though, the proportion of patients with ARF during December was significantly lower (9.1% vs. 58.1% during the rest of the study period; OR, 95% CI: .07, .008–.61, $P = .005$). Diabetes ($n = 26$, 48.1%) and Chronic kidney disease (CKD) stage 3 or greater ($n = 25$, 46.3%) were common. A third of the patients had established CLAD at the time of the diagnosis of COVID-19 ($n = 18$, 33.3%; restrictive: 9; obstructive: 6; mixed: 3). Chest radiographs showed opacities consistent with COVID-19 among a majority ($n = 30$, 55.6%), while CT scans of the chest picked up even more with parenchymal abnormalities (40/46, 87%). A majority of patients who underwent CT scan following a negative chest radiograph (15/18, 83.3%) demonstrated opacities consistent with COVID-19 (Figure 2) reflecting the limited sensitivity of chest radiographs.

Patients were managed based upon a standardized treatment protocol. Almost all patients were admitted to the hospital ($n = 50$, 92.6%; median hospital length of stay: 11 days, 1–137 days). Three of the four patients who were managed as outpatients were approved for monoclonal antibody infusion (only available for outpatients) and recovered, while one patient preferred not to be admitted to the hospital. Nearly a third of the patients had two COVID-19 related hospital admissions (defined as admission within 30 days of onset of clinical symptoms; $n = 16$, 29.6%). All patients were initiated on a multimodality pharmacotherapeutic strategy consisting of antimicrobials (antiviral and antibiotics), anti-inflammatory (steroids and tocilizumab), and

immune augmentation strategies (convalescent plasma, intravenous immunoglobulins and/or bamlanivimab). Figure 3 (upper panel) shows the specific pharmacologic agents used for the management of COVID-19 in the current study group (during the primary admission and readmission for COVID-19). Patients were typically covered with broad-spectrum intravenous antibiotics at admission, which were then de-escalated based on the culture data. Remdesivir was the antiviral agent used among most patients ($n = 44$, 81.5%), and a majority were treated for 10 days ($n = 32$, 59.3%) and was well tolerated. Pulse dose corticosteroids (methylprednisolone 10 mg/Kg IV for 3 days) were administered to 30 patients (55.6%). None of the patients who were tested for antibodies (IgG) against SARS-CoV-2 had evidence of previous exposure/infection ($n = 36$). A majority of the patients were also treated with convalescent plasma ($n = 40$, 74.1%), mostly with a two unit regimen (38/40). None of the patients experienced any side-effects from the convalescent plasma transfusions. Apart from those on chronic anticoagulation with warfarin at presentation ($n = 13$, 24%; Indication: venous thromboembolism among 11 patients and atrial fibrillation among the remaining two) who were continued on the same regimen, patients were started on thromboprophylaxis with once-daily subcutaneous enoxaparin as medical thromboprophylaxis. Bamlanivimab, which became available for clinical use in November 2020, was in limited supply during the majority of the study period, with only five patients receiving approval for its use. Three of these patients recovered after the outpatient infusion and did not need hospitalization,
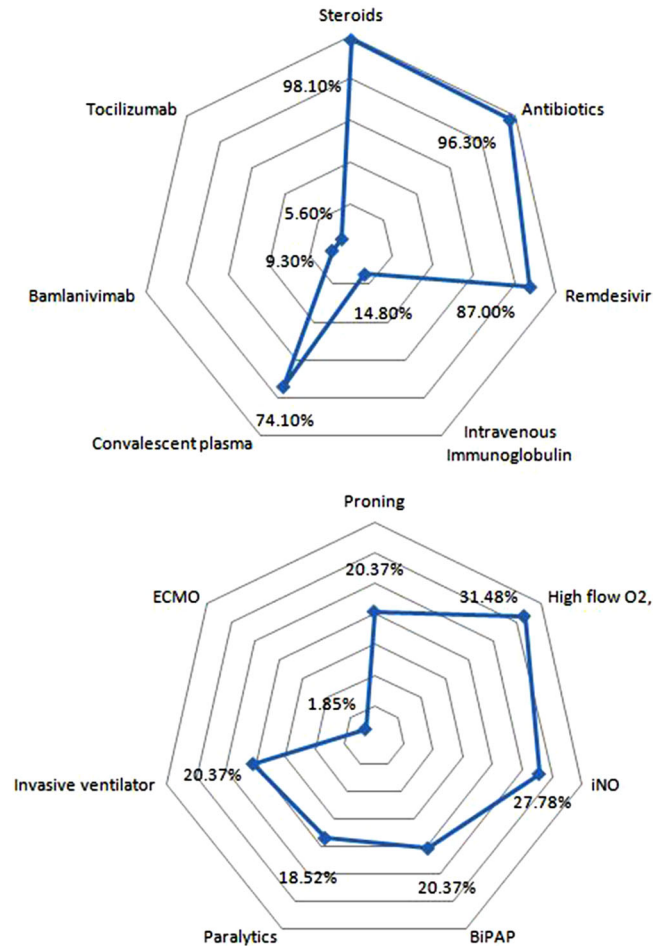
FIGURE 3 Graphs showing the proportion of LT patients with COVID-19 that were treated with various pharmacotherapeutic (upper panel) and respiratory support (lower panel) interventions

FIGURE 4 Multivariate Cox regression survival plots stratified by presence of chronic lung allograft dysfunction (CLAD) at the time of COVID-19 diagnosis among LT patients (adjusted HR: 5.03, 1.14–22.25; $P = .033$). Survival was the dependent variable, and the following covariates were included in the model: age, gender, body mass index, chronic anticoagulation use, and established CLAD

whereas the other two required admission for the progression of their symptoms.

The overall incidence of ARF among LT patients with COVID-19 was 48.1% ($n = 26$). The proportion of patients with ARF during primary admission (22/54; 40.74%) was slightly lower than that during the readmission (8 out of 16 patients who needed readmission, 50%), although half of these patients ($n = 4$) had developed ARF during the primary admission as well. More than half of the patients with ARF needed admission to the ICU ($n = 14$; median length of stay: 15.5 days, 1–74 days). Various respiratory support strategies (as a proportion of overall caseload) utilized during either of the hospital admissions are presented in Figure 3 (lower panel). Self proning was recommended for all patients. Nearly a third needed high flow oxygen, and more than a quarter of the patients were supported via inhaled nitric oxide. The incidence of intubation and mechanical ventilation with rescue therapies was 20.4% ($n = 11$; median length of intubation: 17 days, 2–62 days), and one patient needed extracorporeal membrane oxygenation support. Two patients failed extubation and both of these patients eventually died.

The overall survival from COVID-19 was 85.2% ($n = 46$). The eight patients with mortality attributable to COVID-19 could be divided
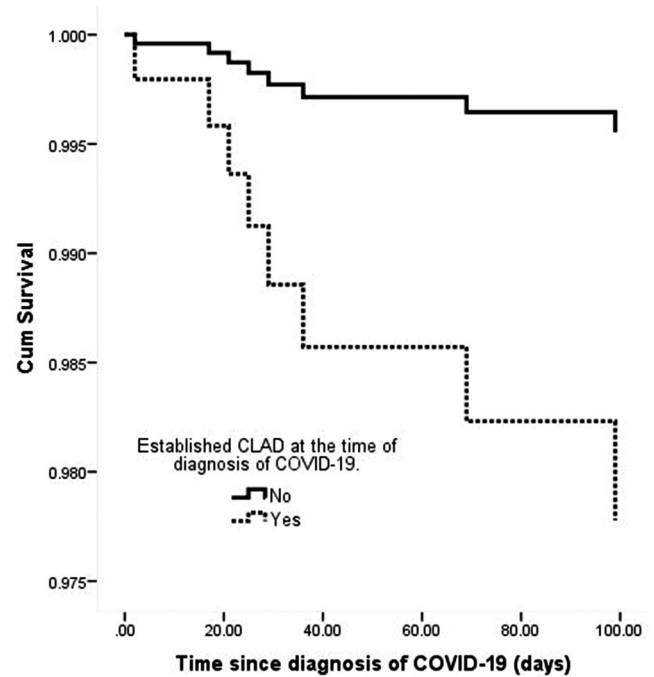
into three major categories. The most common cause of death was ARDS with refractory and persistent hypoxemia ($n = 4$). Two patients improved in terms of ARDS but eventually died of other complications. Finally, the third group consisted of two patients who were electively transitioned to comfort care due to significant comorbidities. While both of these patients developed respiratory failure, neither developed ARDS or MOF.

Baseline variables were compared among survivors and non-survivors. On Cox regression analysis, after adjusting for age, gender, BMI, and chronic anticoagulation use, established CLAD at the time of the diagnosis of COVID-19 emerged as an independent predictor of post-COVID-19 mortality (adjusted HR: 5.03, 1.14–22.25; $P = .033$; Figure 4)

A comparison of patient profiles with and without ARF during the course of COVID-19 is presented in Table 1A–E. Patients with ARF were more likely transplanted for restrictive lung disease and presented with LRT symptoms, including a spirometry decline > 10% (Table 1A–B). The finding of pulmonary opacities was more common among the ARF group, although the difference was not statistically significant. Among the laboratory variables, D-dimer statistically appeared to be most strongly associated with ARF (Table 1C). There were few differences in the proportion of patients treated with various pharmacologic agents (Table 1D) apart from a significantly lower risk of ARF among patients on chronic anticoagulation (7.7% vs. 61%; OR, 95% CI: .05, .006–.45; $P = .001$). A delay in the initiation of convalescent

TABLE 1A Comparative analysis of baseline characteristics among lung transplant patients with new or worsening respiratory failure at any time after SARS-CoV-2 infection

Variable	New or worsening respiratory failure		Odds ratio (95% CI)	P value
	Yes ($n = 26$)	No ($n = 28$)		
Age	60 (20–73)	59.5 (21–72)		.95
BMI at diagnosis (Kg/m^2)	28.2 (17–40)	26.3 (17–35)		.08
BMI > 25 Kg/m^2	84.6%	60.7%	1.39 (.99–1.96)	.07
Male gender	65.4%	71.4%	.76 (.24–2.39)	.77
Caucasian	61.5%	67.9%	.76 (.25–2.32)	.78
Transplant indication (%)				.045
Restrictive	92.3	60.7		
Obstructive	3.8	21.4		
Suppurative	3.8	7.1		
Vascular		10.7		
Bilateral Transplant	76.9%	75%	1.11 (.32–3.88)	1.0
Time since transplant (months)[a]	47.4 (< 1–113)	48 (5–139)		.99
Baseline FEV$_1$ before the infection (L)	2.14 (.69–3.56)	2.35 (.49–4.7)		.24
Baseline FVC before the infection (L)	2.96 (1.17–4.53)	2.9 (1.24–5.21)		.56
Hypertension	92.3%	85.7%	1.33 (.71–2.51)	.67
Hyperlipidemia	73.1%	75%	.95 (.52–1.74)	1.0
Obstructive sleep apnea	42.3%	21.4%	1.69 (.84–3.38)	.14
Coronary artery disease	42.3%	32.1%	1.24 (.7–2.19)	.57
Congestive heart failure	15.4%	7.1%	1.63 (.51–5.19)	.41
Atrial fibrillation	7.7%	10.7%	.69 (.11–4.53)	1.0
Diabetes mellitus	50%	46.4%	1.15 (.4–3.36)	1.0
Co-morbid renal dysfunction[a]	50%	42.9%	1.33 (.46–3.9)	.79
Established CLAD	38.5%	28.6%	1.56 (.5–4.88)	.57

Abbreviations: BMI, Body mass index; FEV$_1$, Forced expiratory volume in 1 s; FVC, Forced vital capacity;.
[a]Defined as CKD-3 or higher.

plasma appeared to be associated with ARF. Expectedly, the outcomes were consistently worse among patients with ARF (Table 1E).

The ROC curve for the peak and trough D-dimer levels during the course of COVID-19 yielded a strong predictive value for ARF (area under the curve: 82%, 95%CI: 64.5–94.5%; Figure 5). Highest D-dimer level of .95 mcg/ml was identified as the best cut-off with a sensitivity of 83.3% and specificity of 78.3%. On multivariate analysis, increased BMI at the onset of COVID-19 (> 25Kg/m^2; adjusted OR: 5.7, .99–32.93; $P = .05$) and D-dimer levels > .95 mcg/ml (adjusted OR: 24.99, 1.77–353.8; $P = .017$) at any time during the course of illness were independently associated with ARF. The use of chronic anticoagulation prior to COVID-19 was independently associated with a lower incidence of ARF (adjusted OR: .024, .001–.55; $P = .02$).

4 | DISCUSSION

Compared to the general population, LT patients appear to be more vulnerable to complications from COVID-19 by virtue of pre-existing comorbidities, an immunosuppressed state, and, perhaps, the host immune response is focused on the allograft itself since the lung is the primary target of the SARS-CoV-2. Despite the advent of safe and effective vaccines, the vulnerability of LT patients remains apparent, with breakthrough infections leading to severe illness, including ARF and death.[13] The findings from the current analysis facilitate a better understanding of the mechanism for ARF among LT patients with COVID-19. More importantly, we identify useful clinical variables and laboratory biomarkers that could form the basis for prognosticating LT patients with COVID-19 and may be instructive in decision-making, such as the need for admission to the hospital or seeking a higher level of care. It appears likely that the COVID-19 pandemic will evolve into an "endemic" infection with continued, albeit attenuated and highly variable, vulnerability to severe disease among vaccinated transplant patients. In such a scenario, prognostication of patients to formulate a customized and proactive management strategy is likely to be the standard of care in the future.

The temporal trends in the COVID-19 cases appear to mimic the national trends (Figure 1).[14] The case curve remained largely flat

TABLE 1B Comparative analysis of characteristics among lung transplant patients with and without new or worsening respiratory failure at presentation for COVID-19

Variable	New or worsening respiratory failure		Odds ratio (95% CI)	P value
	Yes (n = 26)	No (n = 28)		
History of sick contact	57.7%	46.4%	1.57 (.54–4.61)	.43
Duration of symptoms at diagnosis (days)	3 (0–10)	2.5 (0–10)		.39
Lower respiratory tract symptoms at presentation	92.3%	57.1%	9.0 (1.77–45.7)	.005
Spirometry (FEV$_1$ or FVC) decline of > 10%[a]	64.7% (n = 17)	10% (n = 20)	16.5 (2.82–96.62)	.001
Opacities on chest radiograph at presentation	69.2%	46.4%	2.6 (.85–7.92)	.1
Opacities consistent with COVID-19 on CT chest	90.9% (n = 22)	79.2% (n = 24)	2.63 (.46–15.23)	.42
Hospitalization	100%	85.7%		.1
IS regimen				.49
Tacrolimus or cyclosporine	20	24		
Sirolimus	6	4		
IS regimen (CCI)				.42
Azathioprine	2	5		
Mycophenolate	24	23		

Abbreviations: CCI, Cell cycle inhibitor; FEV$_1$, Forced expiratory volume in 1 s; FVC, Forced vital capacity; IS, Immunosuppression.
[a]Patient-reported via the home microspirometers.

TABLE 1C Comparison of laboratory abnormalities during the primary admission among lung transplant patients with and without new or worsening respiratory failure

Variable	New or worsening respiratory failure		P value
	Yes (n = 26)	No (n = 24)	
Lymphocyte count (×10^3/dl)			
At diagnosis	1.2 (.4–2.94)	1.4 (.6–2.6)	.16
Lowest during admission	.16 (0–.46)	.34 (0–.94)	.003
Highest during admission	.88 (.13–3.56)	1.4 (.53–3.36)	.15
Ferritin (mcgm/L)			
At diagnosis	196 (.25–1187)	185.5 (36–1637)	.33
Lowest during admission	268 (56–2213)	143 (15–2627)	.14
Highest during admission	601 (64–6480)	295 (40–3614)	.1
D-dimer (mcg/ml)			
At diagnosis	.47 (.25–1.99)	.6 (.17–32.6)	.43
Lowest during admission	.74 (.21–2.46)	.26 (.17–1.35)	<.001
Highest during admission	1.88 (.26–32.8)	.61 (.09–6.5)	<.001
C-reactive protein (mg/L)			
At diagnosis	5.0 (.4–63.4)	5.0 (.03–59.4)	.79
Lowest during admission	3.45 (.4–192.6)	4.3 (.4–12.2)	.34
Highest during admission	87.5 (5.0–374.5)	35 (2.2–116.6)	.005
Lactate dehydrogenase (U/L)			
At diagnosis	222 (145–376)	191 (124–351)	.11
Lowest during admission	264 (129–653)	212 (131–450)	.29
Highest during admission	436 (5.8–2520)	296 (3.5–727)	.044

TABLE 1D Therapeutic strategies utilized among lung transplant patients with and without new or worsening respiratory failure after COVID-19

Variable	New or worsening respiratory failure		Odds ratio (95% CI)	P value
	Yes (n = 26)	No (n = 28)		
Bamlanivimab	3.8%	14.3%	.24 (.025–2.3)	.35
Remdesivir	84.6%	78.6%	1.5 (.37–6.06)	.73
Duration of Remdesivir				.89
None	4	6		
5 days	7	5		
10 days	15	17		
Time from symptom onset to Remdesivir initiation (days)	4.5 (1–20)	3 (1–16)		.079
Convalescent plasma	76.9%	71.4%	1.33 (.39–4.55)	.76
Time from symptom onset to Convalescent plasma (days)	6 (1–23)	4 (1–8)		.048
Intravenous Immunoglobulin	15.4%	14.3%	1.09 (.24–4.9)	1.0
Pulse corticosteroids	61.5%	50%	1.6 (.54–4.73)	.43
Prednisone taper	69.2%	100%		.002
Anticoagulants				.004
None	None	1		
Coumadin†	1	12		
Heparin (Unfractionated/low molecular weight)	25	15		

†Patients in this group were on chronic anticoagulation at presentation for various indications and were therefore continued on coumadin.

TABLE 1E Outcomes among lung transplant patients with and without new or worsening respiratory failure after COVID-19

Variable	New or worsening respiratory failure		Odds ratio (95% CI)	P value
	Yes (n = 26)	No (n = 28)		
Cumulative length of hospital stay (days)[a]	19.5 (2–137)	10 (0–24)		<.001
Need of ICU admission	46.2%	7.1%	11.1 (2.18–56.98)	.002
Need of ventilator support	42.3%	None		<.001
Survival	69.2%	100%		.001
Need for readmission	34.6%	25%	1.59 (.49–5.15)	.55

[a]Combined length of stay from the primary admission and readmission.

through the early part of the pandemic and the summer months. Notably, the LT population at our center did not experience a summer peak proportional to that seen by the general community in the state of Texas, potentially a consequence of increased vigilance with nonpharmaceutical interventions during this earlier period. The cases started to rise during the fall, but the biggest spike was seen during and after the winter holidays, a period that contributed nearly 80% of the study group.

Interestingly, none of the typical risk factors for severe COVID-19 among the general population such as diabetes, and chronic kidney disease were associated with outcomes in the LT patients. It is indeed possible that the degree of immunosuppression by virtue of being on triple therapy trumps the negative impacts from other risk factors such as diabetes or chronic kidney disease. Furthermore, the high prevalence of most comorbidities among LT patients may also contribute to the lack of association with outcomes after COVID-19.

While the study found a high burden of ARF among LT patients with COVID-19, overall survival was generally higher than in the previously reported series (Table 2).[8,15–23] It is noteworthy that the current series was one of the longest in terms of the duration over which the patients were included which may partially explain better outcomes. It provides an insight into the temporal trends in the outcome of the patients over the duration of the pandemic as our understanding of the disease has improved and therapeutic modalities became available. It

TABLE 2 An overview of the published studies among LT patients with COVID-19

Place of study	Belgium[15]	New York, NY, US[8a]	Switzerland[16]	Germany[17]	Spain[18]	New York, NY, US[19a]	Phila., US[20]	France[21]	UW COVID-19 SOT Registry[22]	Germany[23]	Dallas, TX, US (Current series)
Date published	Jul-20	Aug-20	Oct-20	Oct-20	Oct-20	Nov-20	Nov-20	Jan-21	Aug-21	Oct-21	
Number of lung transplant patients	10	30	1	2	44	32	8	35	120	31	54
Respiratory failure	30%				84%		62.5%				48%
ICU admission	10%		24%	No	30%	34%	37.5%	37.1%	43.7%	58%	25%
Need of mechanical ventilator	10%		19%	None		31%	37.5%	20%	27.5%	26%	20.4%
Mortality	10%	33.30%			39%	34%	25%	14.3%	24.2%	39%	14.8%
Established CLAD					39%	69%		17.1%	13.3%	45%	33.3%
Parenchymal involvement						50-75%	100%				87%
Comments	Age emerged as a predictor		Manifestations of COVID are similar to general population	Fresh transplants with COVID; both did well		100% mortality rate among intubated patients	Two fresh transplant patients with COVID-19. Both of them died.	Overweight status (BMI 25–30 Kg/m²) associated with worse outcomes	As compared ot non-lung SOT, patients with LT have significantly worse survival.	CCI was independent predictor of mortality	Predictors of respiratory failure and survival

Abbreviations: CCI, Charlson comorbidity index; SOT, solid organ transplant.

a 17 patients were common to the two case series from New York, USA.
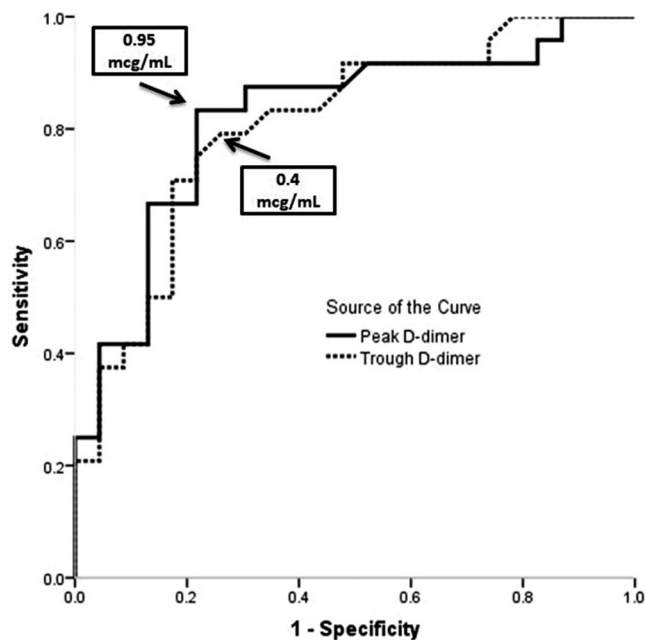
FIGURE 5   Receiver operator characteristic curve to assess the predictive capability of peak and trough D-dimer levels for new or worsening respiratory failure among LT patients with COVID-19. The area under the curve (AUC) for peak D-dimer was 82% (95%CI: 69.5–94.5%), $P < .001$ with .95 mcg/ml as the best cut-off. The AUC for trough D-dimer was 80.8% (68.3–93.3%), $P < .001$ with .4 mcg/ml as the best cut-off

appeared that the proportion of ARF was higher early on and appeared to stabilize in the later part of the pandemic. In addition, patients had a lower risk of readmissions (although the length of stay with primary admission was longer as remdesivir duration was increased to 10 days among patients with CT changes) and were treated earlier with pulse dose corticosteroids during the latter half of the study period. Most deaths occurred among patients infected during the last 3 months of the study (Figure 1), but this was largely driven by the increased number of cases seen during this time period.

During the acute illness, pulmonary parenchymal involvement was seen among a large majority of patients on the CT chest, which is consistent with previously reported findings. Surprisingly, however, the proportion of patients with parenchymal opacities, both on chest radiographs and CT chest, was statistically no different among patients with and without ARF. It is indeed possible that the ARF was driven by mechanisms other than the interstitial involvement, with or with alveolar filling, which is the usual hallmark of viral pneumonia.

Our data suggest that beyond pulmonary infiltrates, vasculopathic changes from coagulation derangements may be a significant driver for allograft dysfunction among LT patients with COVID-19. We found a strong association between peak D-dimer levels and ARF on multivariate analysis; additionally, chronic anticoagulation was protective against ARF, suggesting a possible causal relationship. The association between coagulation defects and poor outcomes among COVID-19 is well established.[24] In fact, an elevated D-dimer has been found to be an independent predictor of mortality among other populations with

COVID-19.[4,7] However, the patterns of coagulation defects among COVID-19 are unique by virtue of a hypercoagulable state.[25] McGonagle and colleagues[26] are credited with proposing the syndrome of pulmonary intravascular coagulopathy (PIC) that seems distinct from disseminated intravascular coagulation (DIC) seen among some critically ill patients. In contrast to DIC, which is a systemic activation of coagulation pathways, PIC is local activation of clotting pathways in the pulmonary microcirculation leading to widespread microthrombi. The key driver of PIC is an intense activation of inflammatory pathways, akin to macrophage activation syndrome, in the alveolar and interstitial compartment. Clinically, PCI manifests as a largely isolated coagulation laboratory abnormality of D-dimer elevation. This paradigm might explain the link between the risk of severe COVID-19 among certain subgroups of patients such as advanced age, male gender, obesity, and diabetes, all of which are independently associated with an increased risk of immunothrombosis. In this regard, LT patients appear highly vulnerable by virtue of the activation of innate and adaptive immune pathways related to their history of transplantation as well as a significantly higher risk of thromboembolic events.[27,28] It is therefore likely that PIC is a significant driver of worse outcomes among LT patients with COVID-19.

A more vexing question related to immunothrombosis pertains to the therapeutic implications of these findings. It appears that anticoagulants can be helpful early on as indicated by the better outcomes among patients on chronic anticoagulation at the time of COVID-19 diagnosis among LT patients. All these patients were on warfarin titrated to maintain an INR level between 2 and 3 and the D-dimer levels at their peak (median with range: .58, .09–2.01 vs. 1.1, .17–32.8) and trough (.26, .17–.77 vs. .57, .17–2.46) were lower. While maintaining such patients on therapeutic doses of warfarin during the acute illness is straightforward, whether to initiate therapeutic dose anticoagulants among patients who are previously not on anticoagulants has been intensely debated. Earlier studies evaluating the use of low molecular weight heparins for thromboprophylaxis did not find a survival benefit, although it seemed to be protective among patients with elevated D-dimer levels.[29] However, the recently published findings from the REMAP-CAP trial confirm the therapeutic benefits of anticoagulation among non-critically ill COVID-19 patients.[30] These findings validate the role of therapeutic dose anticoagulation among non-critically ill LT patients, especially those with elevated D-dimer levels.

The overall survival in the current cohort appears to be better than earlier reports, perhaps reflecting a combination of improvement in the understanding of the disease, availability of pharmacotherapeutic options, and the early institution of multimodality interventions. The French study[21] published earlier this year also reported similar outcomes. Further, the current study found pre-infection CLAD as the only independent predictor of mortality, which is consistent with findings from a multicenter US study.[22] In contrast, a German study[23] did not find an association of pre-infection CLAD with mortality, although this study had a longer follow-up beyond the acute illness from COVID-19. It is indeed possible that CLAD may be a better predictor of survival from acute illness by reflecting the degree of pulmonary reserve, although additional studies are needed to elucidate the true impact

of CLAD on COVID-19 outcomes. The current analysis has some limitations that must be considered while interpreting these results. The study was underpowered as reflected by the wide confidence intervals for the independent predictors. The associations can be prone to confounding by unrecorded variables. We had to limit the number of covariates for the multivariate models due to the sample size, which did not permit fully adjusted associations. Specifically, the association of warfarin use with better outcomes may be related to other patient characteristics, such as their underlying pulmonary condition. Patients with restrictive lung disease were less likely to be on warfarin and had a higher likelihood of ARF. We addressed this issue by adjusting the prediction models for ARF by including patient demographics and transplant indication as covariates to adjust the associations. The study design precludes any conclusions regarding the causality of the association and must await further assessments. Finally, the mechanistic links to explain the association are speculative as prospective studies in this population are sorely lacking.

In summary, the current series provides useful information regarding the burden of ARF among LT patients with COVID-19. While survival has improved since the onset of the pandemic, COVID-19 is associated with significant morbidity among LT patients with likely worsening of the expected post-transplant survival. Patients on chronic anticoagulation seem to enjoy favorable outcomes, while LT patients with an elevated BMI and D-dimer are at risk of ARF.

DATA AVAILABILITY STATEMENT

Data are available on request due to privacy or other restrictions

CONFLICT OF INTEREST

None.

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