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TRANSPLANT INFECTIOUS DISEASE

ORIGINAL ARTICLE

Characteristics and outcomes among vaccinated lung transplant patients with breakthrough COVID-19

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Abstract

Background: Despite multiple studies evaluating the immunological responsiveness to vaccines, the clinical effectiveness of the two-dose mRNA vaccine schedule among lung transplant (LT) patients has not been evaluated.

Methods: We included LT patients who tested positive for SARS-CoV-2 on a nasopharyngeal swab between March 1, 2020, and August 25, 2021 ($n = 70$). The study group was divided based on their vaccination status.

Results: During the study period, 14 fully vaccinated LT patients with one of the mRNA vaccines tested positive for COVID-19 (median age 54, range 30–62 years, M:F 9:5). The vaccinated cohort was younger with bilateral LT, have suppurative conditions as the transplant indication, and present with milder symptoms. However, pulmonary parenchymal involvement was seen among all 12 patients where computed tomography (CT) of chest was available. The laboratory profile indicated a more subdued inflammatory response among the vaccinated group.

A lower proportion of vaccinated patients developed respiratory failure, needed ICU admission or ventilator support, although none of the differences achieved statistical significance. None of the vaccinated patients succumbed to COVID-19 during the study period, while the 4-week mortality among unvaccinated patients was nearly 15% (8/56).

Conclusions: In this cohort of vaccinated LT patients who developed breakthrough COVID-19, the clinical course, risk of complications, and outcomes trended better than unvaccinated patients. However, universal involvement of the allograft demonstrates the continued vulnerability of these patients to significant sequelae from COVID-19. Future studies may evaluate the incremental protection of vaccination after the completion of the third dose of mRNA vaccines among LT patients.

KEYWORDS
allograft dysfunction, CLAD, mRNA vaccines, predictors, SARS-CoV-2, survival

Abbreviation: BMI, body mass index; CCI, cell cycle inhibitors; CLAD, chronic lung allograft dysfunction; COVID-19, Coronavirus disease 2019; CT, computed tomography; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; ICU, intensive care unit; LRT, lower respiratory tract; LT, lung transplantation; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SOT, solid organ transplants; URT, upper respiratory tract

1 | INTRODUCTION

The development of highly safe and effective vaccines against Coronavirus disease 2019 (COVID-19) has been one of the most significant developments in the battle against the SARS-CoV-2 virus.[1–3] The studies among immunocompetent patients have found these vaccines to significantly reduce the risk of infection and severe illness from COVID-19. In contrast, there is little data on the clinical efficacy of vaccines among patients with solid organ transplants (SOT) who are a high-risk group with regard to complications from COVID-19. Furthermore, the risk of adverse outcomes from COVID-19 may not be equivalent among different types of SOT patients. Studies have found that patients with lung transplantation (LT) have a distinctly higher risk for complications from COVID-19.[4] The reasons for this are not clear but felt to be related to the number of comorbidities, level of maintenance immunosuppression (IS), and the allograft itself being the target of the virus among patients with LT.

In the recent months, the data on the rate of seropositivity rates among SOT patients has concerned the transplant community about the lack of antibody response to the mRNA vaccines.[5] This has led to the consideration of the third dose of the mRNA vaccine, which was found to generate a much more robust immunological response among studies evaluating SOT patients[6,7] and received an FDA approval through an emergency use authorization.

Despite multiple studies evaluating the immunological responsiveness to vaccines, there are a limited number of studies evaluating the clinical effectiveness, or lack thereof, of the mRNA vaccines among LT patients. Preliminary studies have mostly reported outcomes among vaccinated SOT patients as a group without differentiating LT and non-LT patients.[8,9] The data among non-LT SOT patients may not be generalizable, given the much worse outcomes among LT patients. Furthermore, earlier studies have been limited by the small number of LT patients, variable study designs, and lack of comparator groups.

The current study was conducted to report the characteristics and outcomes among a cohort of LT patients who were fully vaccinated with two doses of mRNA-based vaccine. We sought to compare the clinical, laboratory, and radiologic characteristics among the vaccinated LT patients with a control group consisting of unvaccinated LT patients with COVID-19 during the earlier part of the pandemic as well as the contemporary group of LT patients who have opted not to vaccinate.

2 | METHODS

This was a single-center retrospective chart review study approved by the UT Southwestern Medical Center Institutional Review Board (# STU-2020-1400). We included all patients in our institution with a history of single or bilateral LT who tested positive for SARS-CoV-2 on a nasopharyngeal swab between March 1, 2020, and August 25, 2021 ($n = 70$) with the study group split on the basis of their vaccination status.

The protocol for testing for SARS-CoV-2 was preformulated and has been described previously.[10,11] While patients underwent screening tests before any procedure or admission to the hospital for other indication per the institutional protocols, no LT patient was diagnosed with COVID-19 in that scenario.

2.1 | Patient management

The lung transplant program at UT Southwestern devised proactive risk mitigation strategies against COVID-19 among LT patients. These included regular electronic communications from the program regarding mask-wearing, hand washing, and social distancing. All routine follow-up care was switched to telehealth-based care, and in-person visits were limited to symptomatic patients. All patients were screened for COVID-19 symptoms before any clinic encounter, and urged to call the program promptly if and when they were exposed to someone with COVID-19 or developed any symptoms concerning for COVID-19.

All patients were encouraged to get COVID-19 vaccinations as soon as the vaccines received US FDA emergency use authorization. Vaccination was delayed for 3 months after undergoing LT or after treatment with antithymocyte globulin and for 1 month after treatment with pulse dose corticosteroid (Methylprednisone 10 mg/Kg IV daily for 3 days). Patients were not tested routinely for a serological response to the vaccination.

The management protocols for COVID-19 were devised at the onset of the pandemic based on the best available evidence, expert guidance, and consensus among the members of the lung transplant team, although with updates as more data became available. Various management strategies, including the details regarding indications for hospitalization, have been described previously.[10]

2.2 | Study definitions

Patients with respiratory symptoms were classified as having upper respiratory tract involvement when the symptoms were limited to rhinitis, cough, or pharyngitis. Those classified with lower respiratory tract (LRT) manifestations presented with productive cough, wheezing, shortness of breath, a decline in spirometry, or opacities on a chest X-ray or computed tomography (CT). A combination of clinical symptoms of LRT involvement and parenchymal opacities consistent with COVID-19 on chest radiographs or CT chest, with or without respiratory failure, defined COVID-19 pneumonia. 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 $PaCO_2$ from baseline hypercapnia signified acute on chronic or worsening respiratory failure. Refractory hypoxemia was defined as the need for rescue measures such as inhaled nitric oxide. Pre-infection chronic lung allograft dysfunction (CLAD) was determined by an independent review of each patient chart by a lung transplant nurse practitioner (LM) and a transplant pulmonologist (AB) using the International Society for Heart and Lung Transplantation criteria.[12]

2.3 | Data collection

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 (IS) regimen at the time of infection, and presenting symptoms. Among the vaccinated patients, we reviewed the time between the vaccination and infection, and the type of vaccine. Pre-infection spirometry (forced vital capacity [FVC] and forced expiratory volume in one second [FEV_1]), laboratory abnormalities including inflammatory markers, and radiological findings were also reviewed. Complications such as COVID-19 pneumonia, new or worsening respiratory failure, admission to the intensive care unit (ICU), ventilator support, and rescue measures for refractory hypoxemia were recorded. Finally, we collected the data on hospital survival.

All patients completed a 4-week follow-up from the time of onset of acute illness.

2.4 | Statistical analysis

Data were described as median with range and proportions as appropriate. We compared the characteristics and outcomes among patients with and without a history of COVID-19 vaccination. The univariate comparison was made using the Fisher's Exact test for categorical and Mann-Whitney *U*-test for quantitative variables. We also analyzed the development of acute or acute on chronic respiratory failure anytime during the course of acute illness as a primary endpoint for the complete study group. We sought to determine the independent association of vaccination status with the development of this complication. Only the pre-COVID-19 characteristics were selected as potential predictor variables. We identified variables associated with the primary endpoint on univariate analysis using the methodology described above. Variables significant at $p < .1$ along with the vaccination status were entered as covariates in a multivariate logistic regression model. Statistical significance was considered at $p < .05$ (two-tailed only).

3 | RESULTS

During the study period, 14 fully vaccinated LT patients tested positive for COVID-19 (median age 54, range 30–62 years, M:F 9:5). All patients were symptomatic for COVID-19. The control group ($n = 56$) comprised of unvaccinated LT patients with COVID-19 during the early part of the pandemic before the vaccines became available ($n = 54$), while two posttransplant patients were diagnosed with COVID-19 after opting against vaccination.

3.1 | Vaccination timeline and breakthrough infections

The earliest patients to get vaccinations were in late December 2020. By the end of February 2021, >60% of the LT population in the program was fully vaccinated. The increasing rates of vaccination among LT patients coincided with a significant reduction in the community transmission nationally during the spring months. Only one patient who had been fully vaccinated was diagnosed with COVID-19 between February and July 2021. However, as the community transmission started to increase in July 2021, breakthrough infections followed, and nearly all of them were diagnosed in the month of August 2021. At the time of the current analysis, there were 388 fully vaccinated LT patients followed in our transplant program (overall prevalence of breakthrough infection: 3.6%).

3.2 | Clinical course of breakthrough infections

The majority of the patients had been vaccinated with one of the messenger RNA vaccines ($n = 13$; 9 patients with Pfizer's BNT162b2 vaccine, and 4 with Moderna's mRNA-1273 vaccine) while one patient had received the J&J's Ad26.COV2.S vaccine. Two of the patients had received the third dose during the previous week before developing COVID-19. All the patients were on standard IS regimen consisting of corticosteroids, calcineurin inhibitors, and cell cycle inhibitors (CCI). The median prednisone dose was 5 mg (range 5–10 mg) while all patients were on tacrolimus with trough levels maintained between 5–10 ng/ml. All patients, except one on azathioprine, were on mycophenolate mofetil (MMF, 92.9%) as the CCI.

All patients were managed per the institutional protocols, and CCI was held for all the patients during the acute illness. Two patients who were not admitted to the hospital presented with mild symptoms after a family member had tested positive. Both were treated with a good clinical response to monoclonal antibodies (casirivimab and imdevimab). Among the remaining 12 patients admitted to the hospital, all were treated with remdesivir for 10 days. Serological testing revealed positive anti-spike IgG antibodies only among six patients at the time of hospital admission, while all the patients were negative for the nucleocapsid antibodies. The clinical course did not seem to be any milder for seropositive patients as two of the six patients developed respiratory failure. In comparison, only one of the eight seronegative patients developed respiratory failure.

The eight seronegative patients (anti-spike antibody) were treated with immune augmentation strategies (casirivimab and imdevimab among three patients while the remaining five patients received two units of convalescent plasma due to the unavailability of monoclonal antibodies for the inpatients). All patients were treated with higher-dose corticosteroids per institutional protocols. One patient with refractory hypoxemia from severe COVID-19 was treated with baricitinib for 10 days (stopped early due to profound cytopenias).

3.3 | Comparative analysis

The baseline characteristics of vaccinated patients with breakthrough infections were different from the unvaccinated patients (Table 1). The vaccinated cohort was younger and more likely to have suppurative conditions as the transplant indication and undergone bilateral LT. The vaccinated patients tended to present with milder symptoms with a

TABLE 1 Comparative analysis of baseline characteristics and outcomes among vaccinated lung transplant patients with breakthrough COVID-19 and unvaccinated historical controls with COVID-19

Variable	Breakthrough infection after COVID-19 vaccination ($n = 14$)	Historical controls with COVID-19 ($n = 56$)	Odds ratio(95% CI)	*p*-Value
Age	54 (30–62)	60 (20–73)		**.018**
BMI at diagnosis (Kg/m^2)	28.9 (21–36)	27.8 (17–40)		.76
Male gender	64.3%	69.6%	0.8 (0.23–2.7)	.75
Race (%)				.95
Caucasian	64.3%	66.1%		
African-American	21.4%	17.9%		
Hispanic	14.3%	14.3%		
Asian/Others		1.7%		
Transplant indication (%)				**.017**
Restrictive	35.7%	75%		
Obstructive	21.4%	14.3%		
Suppurative	28.6%	5.35%		
Vascular	14.3%	5.35%		
Type of transplant				**.03**
Single	None	21.4%		
Bilateral	85.7%	76.8%		
Heart-Lung	14.3%	1.8%		
Time since transplant (months)	45 (13-238)	48 (0.25–139)		.86
Diabetes mellitus	42.9%	50%	0.75 (0.23–2.44)	.77
Co-morbid renal dysfunction†	28.6%	44.6%	0.5 (0.14–1.77)	.37
Established pre-infection CLAD	14.3%	33.9%	0.33 (0.07–1.6)	.2
Lower respiratory tract symptoms at presentation	50%	73.2%	0.37 (0.11–1.22)	.12
Opacities on chest radiograph at presentation	42.6%	55.4%	0.6 (0.18–1.97)	.55
Opacities consistent with COVID-19 on CT chest	100% ($n = 12$)	83.3% ($n = 48$)		.19
Acute or acute on chronic respiratory failure	21.4%	48.2%	0.29 (0.07–1.16)	.08
Remdesivir	85.7%	82.1%	1.3 (0.25–6.76)	1.0
Monoclonal antibodies*	21.4%	14.3%	1.63 (0.37–7.19)	.68
Intravenous immunoglobulin	21.4%	14.3%	1.63 (0.37–7.19)	.68
Convalescent plasma	35.7%	71.4%	0.22 (0.06–0.77)	**.026**
Corticosteroids	100%	100%		1.0
Hospitalization	85.7%	92.8%	0.46 (0.08–2.82)	.59
ICU admission	14.3%	25%	0.5 (0.1–2.51)	.5
Ventilator support	None	19.6%		.1
Survival (4 weeks from acute illness)	100%	85.7%		.34
Persistent oxygen needs at 4 weeks after diagnosis among survivors	7.1%	20.83% ($n = 48$)	0.29 (0.03–2.51)	.43
Survival without need of oxygen at 4 weeks	92.9%	71.4%	5.2 (0.63–43.1)	.16

Abbreviations: BMI, Body mass index; FEV_1, Forced expiratory volume in 1 second; FVC, Forced vital capacity.
†Defined as CKD-3 or higher.
*Bamlanivimab or casirivimab/imdevimab.

lower incidence of LRT symptoms and findings on chest radiographs. However, pulmonary parenchymal involvement was ubiquitous on the CT chest among the vaccinated patients. The pattern of opacities was mostly nodular ground-glass opacities in subpleural location, although two patients in the vaccinated group developed predominantly consolidative opacities with surrounding ground glass (see Figure 1A,B), which contrasted with a predominantly ground-glass pattern among unvaccinated patients (Figure 1C).

The laboratory profile of the two groups is presented in Table 2. Although only a few comparisons achieved statistical significance,

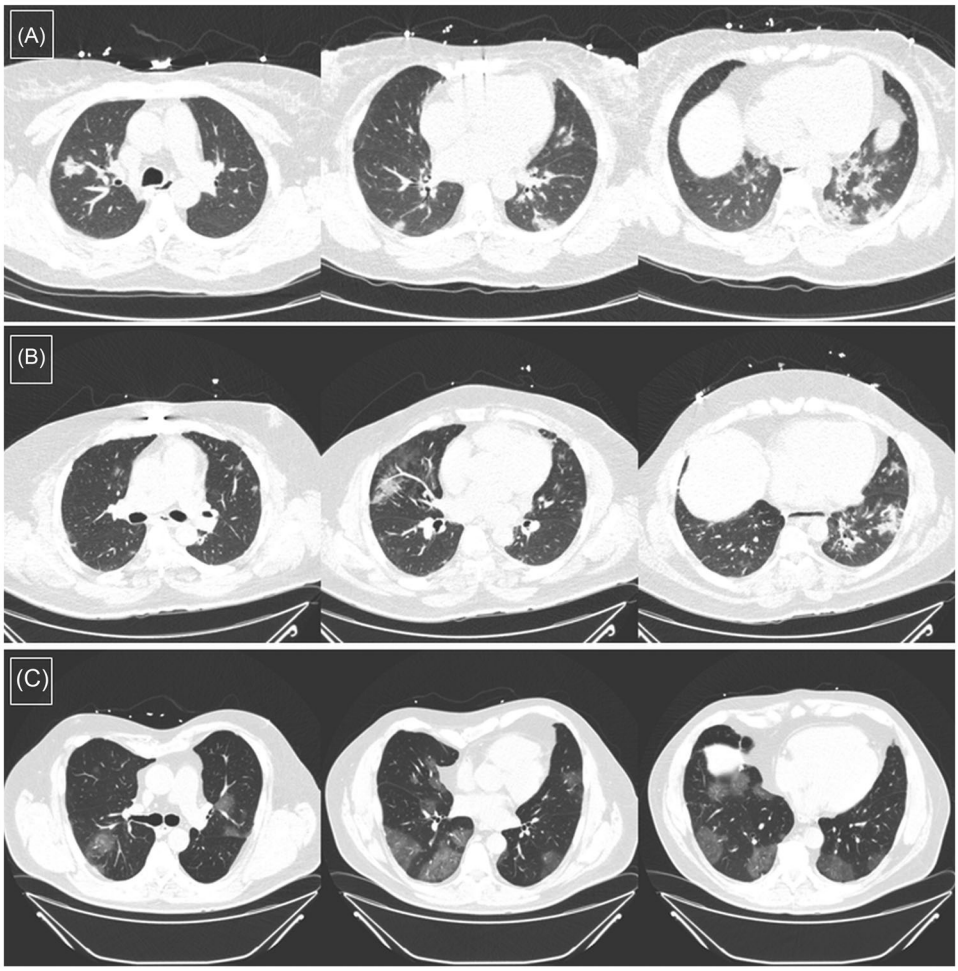

FIGURE 1 (A) CT chest in fully vaccinated patients with breakthrough COVID-19 at day 5 of hospitalization (8 days after symptom onset). (B) CT chest in another fully vaccinated patients with breakthrough COVID-19 at day 5 of hospitalization (9 days after symptom onset). (C) CT chest in an unvaccinated patient with COVID-19 at day 3 of hospitalization (9 days after symptom onset).

patients in the vaccinated group tended to have lower D-dimer and C-reactive protein levels during the course of illness.

3.4 | Outcomes

A majority of the patients were admitted to the hospital in both groups. However, patients in the vaccinated group tended to have overall better outcomes. A lower proportion of vaccinated patients developed respiratory failure or needed ICU admission or ventilator support, although none of the differences achieved statistical significance. Only one vaccinated patient had persistent oxygen needs while one-fifth of the unvaccinated survivors were oxygen dependent at 4 weeks since the acute illness. None of the vaccinated patients succumbed to COVID-19 during the study period, while the 4-week mortality among unvaccinated controls was nearly 15% (8/56).

Given the significance of respiratory failure as an outcome after COVID-19, we sought to identify its predictors. Only the pre-infection characteristics were selected as potential predictor variables. Age, body mass index, transplant indication, pre-COVID-19 diagnosis of CLAD, ongoing use of therapeutic dose anticoagulation (AC) prior to infection, and vaccination status were entered as covariates in a multivariate model (Table 3). The vaccination status did not have an independent association with the development of respiratory failure after COVID-19. However, pre-infection AC use had a strong protective effect (adjusted OR, 95% CI: 0.04, 0.01–0.35, $p = .004$) while higher BMI (adjusted OR, 95% CI: 1.17, 1.02–1.34, $p = .026$) and CLAD (adjusted OR, 95% CI: 6.22, 1.13–34.26; $p = .036$) were associated with an independent increase in the risk of respiratory failure (Table 3).

4 | DISCUSSION

The current study reports one of the largest series of LT patients with COVID-19. We included all the patients diagnosed with COVID-19 in our program during the study period to ensure that various outcomes truly reflected the extent of morbidity and mortality from COVID-19. The study period was extended to the last week of August 2021, which ensured that all the vaccinated patients were within 6 months of being vaccinated. A large proportion of the patients were admitted to the

TABLE 2 Comparative analysis of laboratory abnormalities during the acute illness among lung transplant patients with and without significant spirometry decline after COVID-19. Data presented as median with inter-quartile range

Variable	Breakthrough infection after COVID-19 vaccination ($n = 14$)	Historical controls with COVID-19 ($n = 56$)	p-Value
Lymphocyte count ($X10^3$/dl)			
At diagnosis	1.4 (0.3–2.3)	1.3 (0.39–2.94)	.95
Lowest during admission	0.31 (0–1.97)	0.25 (0–0.94)*	.38
At hospital discharge	0.79 (0.35–2.77)	0.67 (0–3.02)*	.59
Ferritin (ng/ml)			
At diagnosis	173 (32–2634)	183 (82–1637)	.82
Highest during admission	350 (37–2974)	402 (40–6480)*	.73
At hospital discharge	173 (34–671)	261 (22–3720)*	.39
D-dimer (mcg/ml)			
At diagnosis	0.31 (0.17–0.96)	0.55 (0.17–3.26)	**.02**
Highest during admission	1.04 (0.33–7.65)	1.0 (0.1–32.8)*	.73
At hospital discharge	1.05 (0.4–6.8)	1.75 (0.4–31.1)*	.12
C-reactive protein (mg/L)			
At diagnosis	3.15 (0.8–7.3)	5.0 (0.3–63.4)	.61
Highest during admission	29.4 (2.8–229.0)	60.9 (2.2–374.5)*	.41
At hospital discharge	1.0 (0.68–1.9)	5.0 (2–12.2)*	**.019**
Lactate dehydrogenase (U/L)			
At diagnosis	170 (140–341)	216(124–376)	.31
Highest during admission	404 (122–999)	304 (262–2520)*	.49
At hospital discharge	245(197–342)	269 (151–807)*	.52

Notes: Reference range for the laboratory: C-reactive protein <5 mg/L and D-dimer < 0.4 mcg/ml.

hospital given the proactive management protocols[10] and monitoring for the sudden deterioration that sometimes occurs among these patients.

The clinical effectiveness of vaccines may be assessed in multiple ways, including their ability to prevent infection, protection from harboring and spreading the infectious agent, and finally, altering the clinical course favorably among those who do get infected. An additional goal of an ideal vaccine among SOT patients, especially those with LT, should be to mitigate the long-term risk of progressive allograft dysfunction. Our previous work has demonstrated the high incidence of post-COVID-19 lung function loss and development of new CLAD after COVID-19.[11]

Despite several previous studies evaluating the surrogate endpoints to determine the immunogenicity of vaccines among the SOT patients, there are limited data evaluating the clinical effectiveness of the vaccines. The clinical validity of assessing seroconversion or *T*-cell responses as a determinant of the vaccine efficacy against COVID-19 is unproven and not recommended for clinical decision-making.[13] Not only are the different assays designed to assess the humoral or cellular responses after vaccination qualitatively not consistent across different manufacturers, the interpretation of the quantitative assays is even more challenging. The levels of the anti-spike antibodies or the *T*-cell response that provide adequate protection against infection or severe disease remain unknown. Given these limitations, the laboratory markers of immunogenicity must be supplemented with real-world effectiveness studies, and those are sparse. The wide availability of these laboratory markers without a clear understanding of their clinical implications has contributed to significant confusion and frustration among the SOT patients.[14]

The study by Aslan and colleagues is a case in point.[8] They found a nearly 80% reduction in symptomatic infections among the vaccinated SOT patients highlighting the importance of clinical outcomes as the primary endpoint of vaccine effectiveness. It is pertinent to highlight this study's key limitation, which pertains to the lack of randomization. Other studies have looked at the risk of breakthrough infections among vaccinated SOT patients compared to the general population and found a significantly higher risk of breakthrough infections and hospitalization among SOT patients.[15] However, this is more or less predictable as no vaccine can realistically mitigate the risk of getting infected or developing the severe disease among SOT patients to the level of the general population. In fact, the study did find a significant reduction in the incidence of new infections and mortality among vaccinated SOT patients.

Our results also indicate some of the potentially favorable effects of vaccination on the clinical course of COVID-19. Despite few comparisons achieving statistical significance due to the analysis being underpowered, several favorable trends were noted. The vaccinated group had consistently lower levels of inflammatory markers during the acute illness, especially the D-dimer levels, an important marker of coagulation defects that are known to be associated with worse outcomes in

TABLE 3 Predictors of acute or acute on chronic respiratory failure among lung transplant patients with COVID-19 ($n = 70$)

Variable	Respiratory failure		Odds ratio (95% CI)	*p*-Value	Adjusted odds ratio (95% CI)	*p*-Value
	No ($n = 40$)	Yes ($n = 30$)				
Age	58 (21–72)	58.5 (20–73)		.43	1.07 (0.99–1.16)	.1
BMI at diagnosis (Kg/m^2)	27.1 (17.2–36)	29 (17–40)		.05	1.17 (1.02–1.34)	.0026
Male gender	75%	60%	0.73 (0.44–1.21)	.2		
Race (%)				.55		
Caucasian **African-American** **Hispanic** **Asian/Others**	67.5% 20% 10% 2.5%	63.3% 16.7% 20%				
Transplant indication				.008		.07
(%) **Restrictive** **Obstructive** **Suppurative** **Vascular**	52.5% 25% 10% 12.5%	86.7% 3.3% 10%			Ref 0.06 (0.005–0.7) 7.6 (0.39–149.6)	
Type of transplant				.83		
Single **Bilateral** **Heart-Lung**	15% 80% 5%	20% 76.7% 3.3%				
Established pre-infection CLAD	22.5%	40%	1.48 (0.86–2.53)	.1	6.22 (1.13–34.26)	.036
Use of anticoagulation prior to COVID-19†	37.5%	6.7%	0.22 (0.06–0.84)	.004	0.04 (0.01–0.35)	.004
Vaccination against COVID-19	27.5%	10%	0.66 (0.45–0.96)	.08	0.29 (0.03–2.46)	.26

Notes: † Patients on therapeutic dose anticoagulation with warfarin prior to COVID-19 ($n = 17$) for venous thromboembolism ($n = 14$) and atrial fibrillation ($n = 3$).

COVID-19.[16] Furthermore, the vaccinated group may be less likely to develop COVID-19 complications such as respiratory failure, need ICU admission or ventilator support, all of which trended higher among the unvaccinated group. Most importantly, none of the vaccinated patients succumbed to COVID-19.

The key limitation of the current analysis pertains to the matching of the two groups. An important aspect, potentially favorable for the more recent cohort of patients with COVID-19 (vaccinated group) is the assumption that there might be an improvement in management strategies with time. However, the two groups were well matched with regard to the treatment strategies (Table 1) apart from a lower proportion of vaccinated patients receiving convalescent plasma due to the presence of anti-spike antibodies among some of the patients. To further investigate the impact of different phases of the pandemic on the clinical course of COVID-19, we evaluated the outcomes in the latter part of the pandemic (December 2020 to February 2021) among the unvaccinated group. This analysis did not find any differences in the incidence of severe disease or death during the latter phase as compared to the overall unvaccinated cohort thereby discounting the possibility of improvement in management protocols being responsible for better outcomes. On the contrary, the majority of patients seen during the recent months are likely to have been infected with the more infectious and virulent B.1.617.2 (Delta) variant[17,18] that is associated with a higher risk of severe COVID-19. These findings further support the protective effects of the two-dose regimen among LT patients in mitigating the risk of severe disease.

Our analysis has additional limitations. Being a single-center study, results need to be replicated at other centers, perhaps in larger cohorts. The possibility of a higher number of asymptomatic infections among vaccinated patients cannot be excluded although such an occurrence would not alter the overall favorable trends seen in the current analysis. A longer follow-up of patients with breakthrough infections will be important to evaluate any potential benefits of vaccinations beyond the acute illness. This is a significant concern given the high burden of persistent or progressive allograft dysfunction that has been seen among previous studies[11,19] as well as the universal involvement of the allograft seen on CT imaging in the current study. Perhaps, the third dose of the mRNA vaccine may be able to attenuate the clinical severity of the acute illness even further and prevent the long-term pulmonary sequalae. The outcomes among SOT patients fully vaccinated with the three doses may then be benchmarked against those with two doses such as the current cohort to truly elucidate the potential clinical benefit of the much more robust humoral response seen with the three-dose regimen.

In conclusion, we report a series of vaccinated LT patients with breakthrough COVID-19 and contrast their clinical course and out-

comes with the unvaccinated patients. It appears that despite the low seroconversion rates, vaccines may afford some protection against severe clinical disease. However, the universal involvement of the allograft on the CT imaging despite the institution of an aggressive multimodality therapeutic strategy demonstrates the continued vulnerability of these patients. Future studies may evaluate the clinical efficacy of vaccination among LT patients after the completion of the third dose of mRNA vaccines.

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None

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORSHIP PAGE

SB, VK, AB were associated with study design. LDM and AB were associated with data collection and management. AB was associated with data analysis. SB, LDM, PD, MRM, JJ, AL, IT, VK, RLH, LST, CDK, FT, and AB prepared the manuscript.

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