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COVID-19 Vaccination is Associated With Favorable Outcomes Among Lung Transplant Patients With Breakthrough Infections

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ABSTRACT

Background. There are limited data regarding the clinical efficacy of COVID-19 vaccines among lung transplant (LT) patients.

Methods. We included all LT patients diagnosed with COVID-19 between March 1, 2020, and December 10, 2021 (n = 84; median age 55, range, 20-73 years; males 65.5%). The study group was divided into 3 groups based on the vaccination status (patients who did not complete the primary series for any of the vaccines: n = 58; those with 2 doses of messenger RNA (mRNA) or 1 dose of the adenoviral vector vaccine, vaccinated group: n = 16; those with at least 1 additional dose beyond the primary series, boosted group: n = 10).

Results. Pulmonary parenchymal involvement on chest computed tomography scan was less common among the boosted group (P = .009). The proportion of patients with new or worsening respiratory failure was significantly lower among the vaccinated and boosted groups and these patients were significantly more likely to achieve the composite endpoint of oxygen-dependence free survival (P = .02). On multivariate logistic regression analysis, higher body mass index, restrictive lung disease as the transplant indication, and preinfection chronic lung allograft dysfunction were independently associated with acute or acute on chronic respiratory failure while being on therapeutic dose anticoagulation and having received the booster dose had a protective effect.

Conclusion. COVID-19 vaccines appear to have several favorable effects among LT patients with breakthrough infections including lower likelihood of allograft involvement on imaging (among boosted patients), need of hospitalization, and complications such as new or worsening respiratory failure.

DESPITE the development of highly safe and effective vaccines against COVID-19, patients with immune dysfunction from different etiologies have remained vulnerable to breakthrough infections [1]. Among these, patients with history of solid organ transplantation (SOT) are most vulnerable owing to a combination of multiple comorbidities and use of combination immunosuppressive regimen. Indeed, several studies have demonstrated the impaired immunogenicity of mRNA vaccines among SOT patients [2−6] including those with lung transplantation (LT) [6,7]. A concern regarding the lack of adequate

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protection with the two-dose regimen prompted evaluation and eventual approval of the third dose of mRNA vaccines.

Although serologic response is an important predictor of the possible protection against COVID-19, it has several limitations. Protection against COVID-19 is not limited to humoral pathways alone and serologic assessment does not reflect the extent of protection conferred by cellular immunity stimulated by the vaccines. Second, the degree of protection afforded by humoral pathways correlates better with the level of truly neutralizing antibodies, a functional assessment often lacking in studies evaluating the serologic response [8]. Furthermore, specific cut-points for the protective level of antibodies has not been established and the assays themselves have not been validated or standardized across laboratories and are therefore not recommended for clinical use [9]. It is therefore imperative to supplement serologic data with clinical studies evaluating various outcomes of interest among vaccinated SOT patients.

We have previously reported the outcomes among a cohort of vaccinated (2 doses of mRNA or 1 dose of the adenoviral vector vaccine) LT patients with breakthrough COVID-19 [10]. Although there appeared to be trends toward better clinical outcomes among vaccinated patients, we found that the vaccination afforded little protection against the allograft involvement, indicated by development of opacities on the computed tomography (CT) chest during the acute infection. The current study aims to report outcomes among a larger group of LT patients with breakthrough infections while evaluating the incremental benefits of the additional vaccine doses beyond the primary vaccination series. We hypothesized that vaccination provides clinical protection against severe disease among LT patients with breakthrough COVID-19.

MATERIALS AND METHODS

This was a single-center retrospective 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on a nasopharyngeal swab between March 1, 2020 and December 10, 2021 (n = 84) were included. All patients completed at least 4 weeks' follow-up from the time of acute infection. The study group was grouped on the basis of their vaccination status. Patients who did not complete the primary series for any of the vaccines were designated as unvaccinated (n = 58). Patients who completed 2 doses of mRNA or 1 dose of the adenoviral vector vaccine were referred to as the vaccinated group (n = 16), and those who received at least 1 additional dose beyond the primary series were designated as boosted (n = 10).

The protocol for testing and management for COVID-19 was preformulated and has been described previously [10,11]. While patients underwent screening tests before any procedure or admission to the hospital for other indications, none of the patients in the current series were diagnosed in that fashion. Vaccination was deemed effective 2 weeks from the day of the second and third dose among the vaccinated and boosted patients, respectively. Our protocols for vaccination also have been described previously [10].

Patients were classified as having lower respiratory tract manifestations if they presented with productive cough, wheezing, shortness of breath, a decline in spirometry, or opacities on a chest x-ray or CT. 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. Two investigators (L.M. and A.B.) conducted an independent review of each patient chart to determine the diagnosis of preinfection chronic lung allograft dysfunction (CLAD) using the International Society for Heart and Lung Transplantation (ISHLT) criteria [12].

Qualitative serologic testing for antispike antibodies became available for clinical use in May 2021. Patients were not tested routinely after vaccination unless they were diagnosed with COVID-19 (n = 30), and the testing was done at the time of their diagnosis. Some of the patients, mostly after the emergence of the B.1.617.2 (Delta) variant, underwent sequencing for the type of the variant (n = 19) with majority confirmed as delta (18 of 19). Among the remaining patients, the infecting variant was adjudicated based the predominantly circulating variant using a predefined threshold. Specifically, patients were presumed to be infected with the most prevalent variant, when the test was performed in a timeframe when it was being sequenced among >97% of the isolates in circulation.

Statistical Analysis

Data were described as median with interquartile range (IQR) and proportions as appropriate. We conducted a three-way comparison to compare different variables based on the vaccination status (unvaccinated, vaccinated, and boosted). The univariate analysis included the Fisher's Exact test for categorical variables and Kruskal-Wallis H test for quantitative variables.

We sought to determine if vaccination protected against severe disease. To address this objective, we analyzed the development of acute or acute on chronic respiratory failure anytime during the course of acute illness as a primary endpoint. We selected patient demographics, and their vaccination status in addition to the preinfection characteristics that were significant on univariate analysis at $P < .1$ as potential predictor variables. With acute or acute on chronic respiratory failure as the dependent variable, we entered these covariates in a multivariate logistic regression model to assess independent association of vaccination status and respiratory failure after COVID-19. Receiver operator characteristics (ROC) curve were constructed to assess the performance of quantitative variables identified as predictors of respiratory failure and to determine the best cut-off value.

Postinfection survival was analyzed as the secondary endpoint. Patients were followed until death or January 15, 2022, whichever was later. With a similar methodology as described above, covariates were selected and analyzed using the Cox proportional hazard modeling to identify independent predictors of post-COVID survival.

Statistical significance was considered at $P < .05$ (two-tailed only).

RESULTS

A majority of the patients in the program were vaccinated at the time of this report (>94%). Among the 437 patients followed in the program, 21 remain unvaccinated while another 5 patients have had only 1 dose of the mRNA vaccine (proportion of unvaccinated patients: 5.9%). Among the remaining patients, the majority (318 of 411, 77.4%) had been boosted and received 3 or more doses of one of the mRNA vaccines.

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

		Breakthrough Infection After COVID-19 Vaccination		
Variable	Unvaccinated Patients With COVID-19 (n = 58)	Vaccinated (n = 16)	Vaccinated and Boosted (n = 10)	*P* Value
Age	58.5 (55-65)	52.5 (43-59)	52 (41-60)	.015
BMI at Diagnosis (kg/m^2)	27.9 (25-32.8)	28.9 (24.5-31)	27.3 (24.2-30.3)	.835
Male Sex (%)	69	56.3	60	.59
Race (%)				.99
White	65.5	68.8	70	
African-American	17.2	18.7	20	
Hispanic	15.5	12.5	10	
Asian/Others	1.7			
Transplant Indication (%)				.053
Restrictive	74.1	31.3	60	
Obstructive	13.8	25	10	
Suppurative	6.9	25	10	
Vascular	5.2	18.7	20	
Type of Transplant (%)			100	.13
Single	20.7	6.3		
Bilateral	79.3	93.8		
Diabetes Mellitus (%)	51.7	43.8	30	.42
Comorbid Renal Dysfunction* (%)	44.8	37.5	80	.08
Established Preinfection CLAD (%)	34.5	18.8	20	.37
Lower Respiratory Tract Symptoms at Presentation (%)	72.4	56.3	60	.71
Opacities on Chest Radiograph at Presentation (%)	56.9	43.8	30	.22
Opacities Consistent with COVID-19 on CT Chest† (%)	84 (n = 50)	92.9 (n = 14)	44.4 (n = 9)	.009
Type of Variant (%)			100	< .001
Wuhan	94.8	6.25		
Delta	5.2	93.75		
Acute or Acute on Chronic Respiratory Failure (%)	50	25	10	.022
Remdesivir (%)	82.8	87.5	60	.18
Duration of Remdesivir (%)				.24
5 d	25	21.4	50	
10 d	75	78.6	50	
Monoclonal Antibodies‡ (%)	13.8	18.8	50	.03
Intravenous Immunoglobulin (%)	13.8	18.8	None	.37
Convalescent Plasma (%)	70.7	37.5	10	< .001
Corticosteroids (%)	100	100	100	1.0
Hospitalization (%)	93.1	87.5	60	.012
ICU Admission (%)	27.6	18.8	10	.42
Ventilator Support (%)	22.4	6.3	None	.09
4-wk Survival (%)	86.2	93.8	100	.35
Survival Without Persistent Oxygen Needs (%)	63.8	87.5	100	.02

BMI, body mass index; CLAD, chronic lung allograft dysfunction; CT, computed tomography; ICU, intensive care unit.

* Defined as CKD-3 or higher.

† All patients underwent CT chest during the first 2 weeks of acute illness.

‡ Bamlanivimab or casirivimab/imdevimab.

Study Group

During the study period, 84 LT patients tested positive for COVID-19 (median age 55, range, 20-73 years; males 65.5%). All patients were symptomatic for COVID-19. Since the vaccines became available to the LT patients around 1 year ago, a majority of infections occurred among vaccinated (n = 16) or boosted patients (n = 10) while 4 unvaccinated patients have developed COVID-19. Apart from these 4 patients, the unvaccinated group included an additional 54 patients who developed COVID-19 before the availability of vaccines.

Apart from 2 patients in the vaccinated group, the rest were within the 6 months of the effective date of their last vaccine dose (2 weeks after the dose). The median time from the effective date of last vaccine dose to infection was significantly shorter in the boosted group as compared with the vaccinated group (57 days, IQR 54.5-73 days vs 162.5 days, 128.75-185 days; $P < .001$).

A majority of breakthrough infections seemed to coincide with the local community transmission especially during the latter half of the year with the emergence of Delta variant. The cumulative number of infections was similar to that seen during

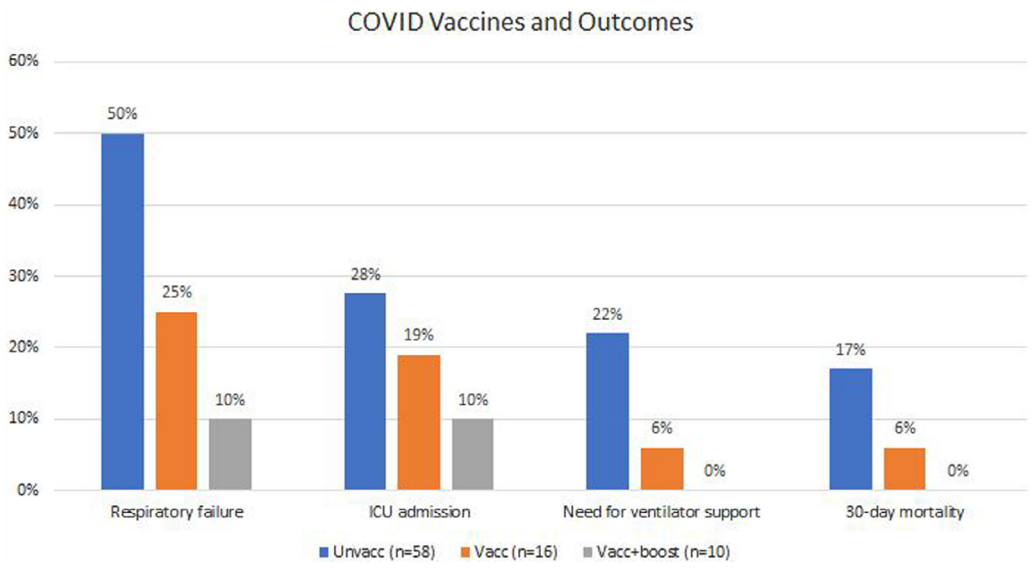

Fig 1. Outcomes among the 3 groups based on the vaccination status.

the prevaccination era in 2020 (25 infections were diagnosed from the onset of pandemic to December 15, 2020). Except for one boosted patient diagnosed in the second week of December 2021, all infections occurred before the emergence of the B.1.1.529 (Omicron) variant. This patient was tested for the type of SARS-CoV-2 variant and confirmed to be infected with the Delta variant.

A majority of the patients had been vaccinated with the mRNA vaccines (n = 25), 19 patients with BNT162b2 (Pfizer-BioNTech COVID-19 vaccine), and 6 with mRNA-1273 (Moderna COVID-19 vaccine), and 1 patient had received the Ad26.COV2.S (Janssen/Johnson & Johnson COVID-19 vaccine). All patients were on standard immunosuppressive 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 the tacrolimus with trough levels maintained between 5 and 10 ng/mL. The majority of the patients with breakthrough infections were on mycophenolate mofetil (92.3%) as the CCI, and 1 patient each from the vaccinated and boosted groups were on azathioprine.

Patient management. All patients were managed per the institutional protocols with augmentation of corticosteroids, transient cessation of the CCI, and symptomatic management during the acute illness. Hospitalized patients were started on antiviral agent (remdesivir) along with immune augmentation with intravenous immunoglobulin or convalescent plasma. Patients with upper respiratory tract with or without mild constitutional symptoms were managed from the outpatient (n = 10, 12%) with a lower proportion of patients needing hospitalization in the boosted group (Table 1). Regardless of the seropositivity, efforts were made to treat patients with monoclonal antibodies directed at the spike protein of the SARS-CoV-2 (bamlanivimab or casirivimab/imdevimab) although access to these medications was limited (n = 16, 19%).

Expectedly, all 4 of the unvaccinated patients who were tested for antispike antibodies were negative. Among the vaccinated patients, serologic testing was positive only among a minority (8 of 26, 30.8%). The seroconversion rates in the boosted group (20%) were lower than the vaccinated group (37.5%). The clinical course did not seem to be any milder for seropositive patients, as 3 of the 8 patients, including 1 boosted patient, developed respiratory failure. In comparison, only 2 of the 18 seronegative patients developed respiratory failure among the vaccinated or boosted patients.

Comparative Analysis Based on the Vaccination Status

Various baseline characteristics and outcomes among the 3 study groups are compared in Table 1. The vaccinated and boosted patients tended to present with milder symptoms with a lower incidence of lower respiratory tract symptoms and imaging abnormalities. The incidence of parenchymal involvement on the chest CT was lower in the boosted group as compared with the vaccinated and unvaccinated groups.

The boosted group had consistently better outcomes than the other 2 groups (Table 1; Fig 1). Boosted patients were less likely to be hospitalized while the proportion of patients with acute or acute on chronic respiratory failure was significantly lower among the vaccinated and boosted groups. The need for intensive care unit admission, ventilator support, and mortality also trended lower among vaccinated and boosted groups. Finally, the vaccinated and boosted patients were significantly more likely to achieve the composite endpoint of oxygen-

Table 2. Predictors of Acute or Acute on Chronic Respiratory Failure Among Lung Transplant Patients With COVID-19 (n = 84)

Variable	Respiratory Failure		Odds Ratio (95% CI)	*P* Value	Adjusted Odds Ratio (95% CI)	*P* Value
	No (n = 50)	Yes (n = 34)				
Age	56.5 (49-63)	58 (55-62)		.26	1.06 (0.98-1.14)	.13
BMI at Diagnosis (kg/m^2)	26.7 (23.5-29.8)	29.8 (26.9-34.8)		.009	1.16 (1.03-1.31)	.014
Male Sex (%)	72	55.9	0.49 (0.2-1.23)	.16		
Race (%)				.48		
White	70	61.8				
African-American	18	17.6				
Hispanic	10	20.6				
Asian/Others	2					
Transplant Indication (%)				.008	Reference	
Restrictive	52	82.4			0.11 (0.02-0.74)	.02
Obstructive	22	5.9			3.6 (0.3-43.47)	.31
Suppurative	10	11.7				
Vascular	16					
Type of Transplant (%)				0.83		
Single	15	20				
Bilateral	80	76.7				
Heart-Lung	5	3.3				
Established Preinfection CLAD (%)	22	41.2	2.48 (0.95-6.46)	.09	4.78 (1.13-20.24)	.034
Type of Variant (%)				.16		
Wuhan	60	76.5				
Delta	40	23.5				
Comorbid Renal Dysfunction (%)	46	50	1.17 (0.49-2.81)	.83		
Diabetes Mellitus (%)	42	55.9	1.75 (0.73-4.22)	.27		
Use of Anticoagulation Before COVID-19* (%)	34	5.9	0.12 (0.026-0.57)	.003	0.04 (0.005-0.34)	.003
Azathioprine as the Cell Cycle Inhibitor (%)	16	8.8	0.51 (0.12-2.07)	.51		
Vaccination Against COVID-19 (%)				.02	Reference	.43;
Unvaccinated	58	85.3			0.49 (0.09-2.84)	.048
Vaccinated	24	11.7				
Boosted	18	3			0.07 (0.05-0.97)	
Lower Respiratory Tract Symptoms at Presentation (%)	54	88.2	1.8 (1.31-2.47)	.001		

CLAD, chronic lung allograft dysfunction.

* Patients on therapeutic dose anticoagulation with warfarin before COVID-19 (n = 19) for venous thromboembolism (n = 14) and atrial fibrillation (n = 5).

dependence free survival after COVID-19. The only vaccinated patient to succumb to COVID-19 during the study period had not received their booster dose and was beyond 6 months from the last vaccination dose.

Predictors of Outcomes

We initially analyzed acute or acute on chronic respiratory failure as the dependent variable with preinfection characteristics as potential predictor variables (Table 2). In this analysis, age, body mass index (BMI), transplant indication, pre-COVID-19 diagnosis of CLAD, ongoing use of therapeutic dose anticoagulation before infection, and vaccination status were entered as covariates in a multivariate model (Table 2). Higher BMI, restrictive lung disease as the transplant indication, and preinfection CLAD were independently associated with respiratory failure after COVID-19 whereas therapeutic dose anticoagulation at the time of infection had a protective effect. With the unvaccinated group as the comparator, the boosted group was independently associated with lower risk of respiratory failure. The BMI had a modest area under the curve on the ROC curve analysis for predicting respiratory failure (Fig 2) with 27 kg/m^2 as the best cut-off.

The analysis for post-COVID-19 survival using the Cox-proportional hazards model revealed female sex (adjusted hazard ratio, 95% CI 4.8, 1.42-16.1; P = .012) and pre-infection CLAD (6.94, 2.05-23.8; P = .002) as independent predictors of adverse outcomes (Fig 3).

DISCUSSION

The current study builds on our previous work on outcomes among LT patients with COVID-19. We focused on further elucidating the clinical benefits of COVID-19 vaccines among LT patients who are the highest risk group among SOT patients. Specifically, we were able to evaluate the incremental benefit of booster dose after two-dose regimen of mRNA vaccines on various clinical endpoints. In addition, we sought to evaluate for an independent association of vaccination with respiratory failure and survival after COVID-19.

The lack of SOT patients among the pivotal trials on safety and efficacy of COVID-19 vaccines along with lower seroconversion rates among SOT patients after vaccination has heightened the concerns regarding the clinical effectiveness of vaccines. Furthermore, studies evaluating patients with breakthrough infections have found the presence of pre-existent immune dysfunction [1,13,14], including history of SOT, as a major risk factor. This may have contributed to significant vaccine hesitancy among SOT patients [15]. However, the clinical studies on the efficacy of COVID-19 vaccines among SOT patients have started to emerge and appear to demonstrate their beneficial effects. In a large population-based study from United Kingdom, mortality among SOT patients was reduced from 12.6% among unvaccinated individuals to 7.7% among those with 2 vaccine doses. The 2 single-center studies by Aslan et al also found that, independent of age, sex, and time since

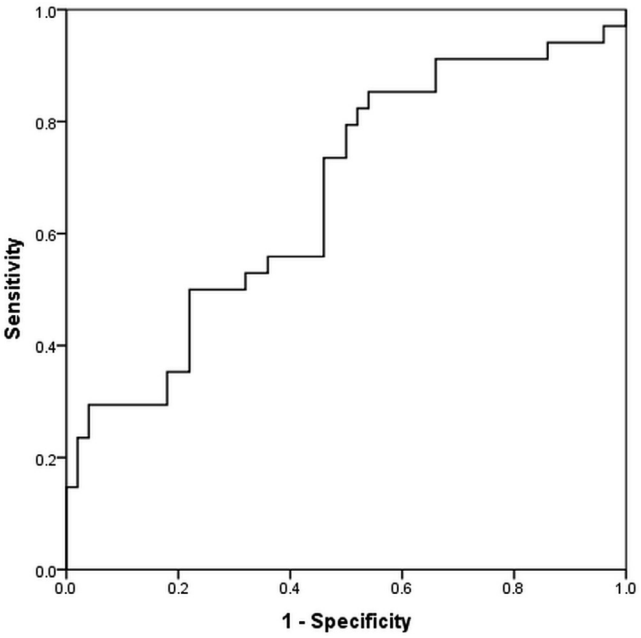

Fig 2. Receiver operating characteristics curve for body mass index at the time of infection with acute or acute on chronic respiratory failure as the dependent variable. The area under the curve was 66.9% (CI 55%-78.8%; *P* = .009). A body mass index of 27 kg/m^2 was determined to be the best cut-off resulting in sensitivity of 73.5% and specificity of 50% for prediction of respiratory failure after COVID-19 among lung transplant patients.

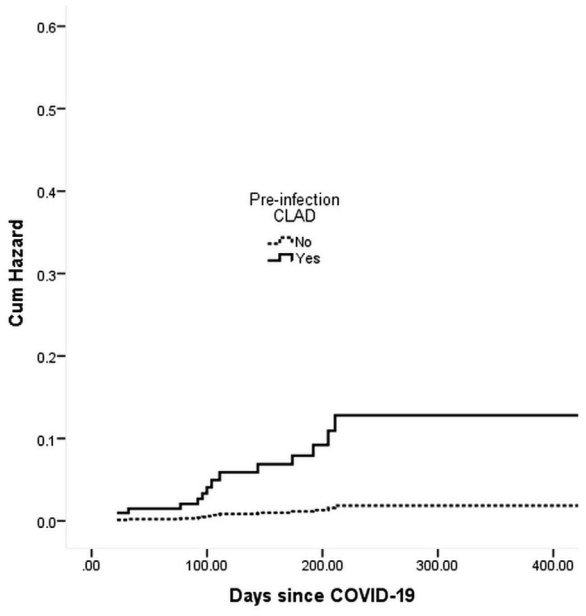

Fig 3. Multivariate Cox regression plots stratified by the presence of chronic lung allograft dysfunction at the time of COVID-19 diagnosis among lung transplant patients (adjusted HR: 6.94, 2.05-23.8; *P* = .002). Post-COVID-19 survival was the dependent variable and following covariates were included in the model: age, sex, body mass index, transplant indication, chronic anticoagulation use, vaccination status, and established chronic lung allograft dysfunction.

vaccination or transplantation, 2 doses of mRNA vaccination were associated with a significant reduction in the development of symptomatic COVID-19 [16,17]. We have also previously reported our experience of vaccinated LT patients with breakthrough COVID-19 who seemed to experience a milder clinical course [10]. Although the current analysis reinforces the findings from the earlier study, the favorable effect of vaccines was more convincing. This was likely driven by a combination of higher vaccine efficacy in the boosted group along with an increased statistical power given the large sample size.

In addition to protection from acquiring infection and reducing risk of severe disease, an important goal of vaccination among SOT patients, especially those with LT, is to mitigate the risk of allograft dysfunction. Our management protocols used radiological involvement of the allograft on CT chest as a surrogate marker for increased risk of complications. Indeed, preliminary data link radiological abnormalities with worse outcomes after COVID-19 among LT patients [18,19]. However, one of the important findings from our previous analysis was the failure of a two-dose vaccine regimen to protect against allograft injury. This was evident in the current analysis also where the vaccinated group had a similar burden of opacities on CT chest during the acute illness. Nevertheless, the boosted group had a significantly lower incidence of parenchymal involvement on CT chest indicating a higher level of protection against allograft injury from COVID-19.

Another interesting finding from the current analysis pertains to the lack of association of seroconversion with outcomes after breakthrough infections. This finding highlights the limited role of serologic testing in predicting the clinical course and argues against customizing management strategy based on

seropositivity. This is especially pertinent when considering passive immune augmentation modalities such monoclonal antibodies for prophylactic or therapeutic indication.

There are some important limitations of the current analysis. The baseline characteristics were not matched among the 3 groups. We addressed this limitation by including age and transplant indication as covariates in the multivariate analyses, and the protection against respiratory failure among boosted group was independent of these potential confounders. Another important aspect, potentially favorable for the more recent cohort of patients with COVID-19 (vaccinated and boosted groups), is the assumption regarding improvement in management strategies with time [20]. An important difference in this regard was a significantly higher proportion of boosted patients receiving monoclonal antibodies. However, the key driver for this finding was the milder presentation and lower incidence of hospitalization among boosted patients as monoclonal antibodies were not available for inpatient use. In contrast, a significantly lower proportion of boosted patients were treated with remdesivir and convalescent plasma as the immune augmentation strategy, treatment modalities only accessible to hospitalized patients. Furthermore, the survival advantage among patients with COVID-19 during the later months of the pandemic is likely nullified with the emergence of progressively more infectious and virulent strains. In this regard, all the vaccinated and boosted patients were confirmed or adjudicated to have been infected with the Delta variant, which is associated with higher risk of severe COVID-19 [21,22]. Finally, the time between the vaccine effectiveness and breakthrough infections was significantly longer in the vaccinated group, which may also contribute toward better outcomes among the boosted patients.

We conclude that COVID-19 vaccines may have several favorable effects among LT patients with breakthrough infections. These encompass turning the disease into a milder form with lower likelihood of hospitalization, and complications such as new or worsening respiratory failure as well as oxygen-dependence free survival after COVID-19. The use of booster dose may protect against radiologic allograft involvement and is independently associated with a lower risk of respiratory failure after COVID-19.

DATA AVAILABILITY

Data will be made available on request.

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