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Low Mortality Associated with COVID-19 Infection in Lung Transplant Recipients at a Single Center

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Abstract

Lung Transplant Recipients (LTR) are particularly vulnerable to severe infection, hospitalization, and death due to community acquired respiratory viruses. As a result, the global SARS-Cov-2 pandemic poses a higher risk to this population. We aim to study the lung function, severity of infection and mortality among LTR at a single center. A retrospective chart review was performed on all LTR at the University of San Diego, California Medical Center between June 2020 and September 2022. Spirometry was performed at 1-2 months and then again 3 months after infection. Patients were closely monitored for the development of acute cellular rejection (ACR). 72 LTR were infected with COVID-19. 37.5% required hospital admission, of which 25.9% required management in the intensive care unit (ICU). 73.6% LTR had received at least one vaccination dose prior to infection. Post-infection, the median drop

in FEV1 was 140 mL and FVC was 25 mL within 1-2 months. At 3 months post-infection the median reduction in FVC was slightly larger at 75 ml, while median decline in FEV1 decreased to 55 ml. Overall, the rates of ACR and mortality in this population were both 4.2%. Additionally, monoclonal antibody (mAb) therapy reduced hospitalization (20.9% vs 62%) and mortality (0% vs 10.3%), Our study found low rates of ACR and mortality in LTR with confirmed COVID-19, despite the statistically significant decline in FEV1, and trends with FVC. The use of vaccinations and mAb therapy decreased rates of hospitalizations, with mAb therapy reducing mortality as well.

Keywords
Lung Transplant; COVID-19; Sars-Cov-2

1. Introduction

To date, the severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) global pandemic has been responsible for over 650 million cases and 6.5 million deaths worldwide [1]. Lung transplant recipients (LTR) are at particularly high risk for complications from coronavirus disease 2019 (COVID-19) due to their immunocompromised status and by virtue of the lung being the primary site of infection. Available data on the short-term effect of COVID-19 in lung transplant recipients remains limited [2-4]. As the pandemic has progressed, several new viral variants have emerged, with several time periods dominated by different variants, demarcating viral 'eras'. The outcomes associated with the various viral variant eras of COVID-19 in LTRs are not well characterized.

Mortality rates for LTRs who contracted COVID-19 infection ranged from 8-39% in observational case series [2, 4-13] In fact, current literature reports up to 8 times higher mortality rates associated with COVID in recipients of solid organ transplants, when compared to the general population [14]. Most of the observational studies on LTR with COVID-19 are from the earlier COVID-19 variant eras of the pandemic at which point treatment modalities were substantially more limited than there are available today. Currently available literature document short term follow ups and allograft dysfunction after COVID-19 infection has not been reported. Several community acquired respiratory viral infections, such as respiratory syncytial virus (RSV), are associated with an increased risk of acute cellular rejection (ACR) and chronic allograft rejection (CLAD) but such data regarding COVID-19 is lacking [15]. The initial management goal of LTRs with COVID-19 infection is to allow for adequate degree of cellular immunity to combat infection while minimizing the risk of increased allogeneic response triggering allograft rejection.

Our aim in this study is to expand the current understanding of disease progression among LTRs with COVID-19 and characterize outcomes, based on COVID-19 viral variant eras, vaccination status and the use of pre- and post-exposure therapies.

2. Methods

All LTR aged 18 years or older who had confirmed infection with a positive polymerase chain reaction (PCR) for SARS-CoV-2 in an inpatient or outpatient setting between June, 2020 and September, 2022 were retrospectively reviewed for descriptive observation at the University of

California, San Diego. This study was reviewed and approved by the Institutional Review Board (IRB #210245). Informed consent was waived due to the retrospective nature of the study. This study complies with the LIDSEN Journals' ethics guidelines.

Patient demographic data, including age, co-morbidities, type and timing of transplantation, and type of immunosuppression were documented. Symptoms at time of diagnosis and outcomes including hospitalization, changes in lung function, and mortality were characterized. Radiographic findings at the time of diagnosis of COVID-19, modifications to immunosuppression, vaccinations, and treatment for COVID-19 were characterized. If hospitalized, the level of care, degree of supplemental oxygen requirement or mechanical ventilatory support and length of stay were recorded. Therapeutic drug levels were determined according to our UCSD lung transplant protocols unless a different goal was specified by a lung transplant provider in the last clinical note prior to COVID-19 infection.

Patients had spirometry done approximately 6 weeks post COVID-19 infection. If there was evidence of a significant decline in spirometry, persistent respiratory symptoms or non-resolving infiltrates on chest imaging then patients were referred for flexible fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy to assess for rejection or superimposed infection. Spirometry data for all patients were reviewed to ensure all data met American Thoracic Society criteria for pulmonary function testing [16]. Diagnosis of chronic lung allograft dysfunction (CLAD) was determined based on the ISHLT guidelines with an assessment of the spirometry values and computed tomographic (CT) images of the chest [17]. Determination of radiographic opacities was based on the final read made by the attending radiologist. Pathologic grading of rejection was based on the working formulation for the standardization of nomenclature in the diagnosis of lung transplant rejection as determined by the pathologist based on the ISHLT guidelines [18].

Unfortunately, routine viral sequencing is not common practice, so exact data on viral variant within our patient population was not obtainable. However, utilizing widely recognized dates of dominant variant timelines, supported by Center for Disease Control (CDC) data, we delineated viral "variant eras" based on the date of positive PCR test. Based on CDC data, we identified three COVID-19 variants dominated during our study period. The wild-type COVID-19 variant served as the dominant species between June 2020 and May 2021. The Delta variant dominated from June 2021 until December 2021, and was followed by the Omicron variant from January 2022 until the completion of the study period in September 2022 [19, 20].

In the United States, the Food and Drug Administration (FDA) released the first COVID-19 Vaccination Emergency Use Authorization on December 11, 2020, with the Advisory Committee on Immunization Practices of the CDC releasing guidelines for vaccination of all persons over the age of 16 on the same date. On September 22, 2021, the CDC would go on to release recommendations for people to receive a booster dose, in addition to the primary series of vaccinations.

2.1 Comorbidity Definitions

Our patients' comorbidities were diagnosed utilizing commonly observed definitions. For chronic kidney disease (CKD), we utilized the Kidney Disease Improving Global Outcomes (KDIGO) definition of CKD. Our heart failure patients met current American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the diagnosis. We defined obesity as a body mass index equal to or greater that 30 kg/m^2, in accordance with World Health Organization guidelines. The Eighth

Joint National Committee (JNC 8) guidelines were utilized for hypertension diagnosis and current American Diabetes Association guidelines for the diagnosis of diabetes mellitus.

2.2 Statistical Analysis

Demographic characteristics as well as baseline measurements were reported as counts with percentages, or median with interquartile range of measurements for categorical values with continuous variables. Statistical significance of impacts on outcomes including hospitalization and mortality were determined by performing Mann Whitney U tests for continuous variables and Chi Square analyses for categorical variables. The change in spirometry results were compared with pre-COVID baselines utilizing Paired Wilcox testing. All statistical analyses were performed using R 4.2.2 software. A p value less than 0.05 was utilized as the cut off to reject the null hypothesis.

3. Results

3.1 Patient Characteristics

Among 236 total LTR, 72 (30.5%) were identified in the study period with confirmed COVID-19 with baseline characteristics as noted in Table 1. The median age was 53.5 years old, 62.5% were men, and 54.2% were Caucasian. The majority (77.8%) had undergone bilateral lung transplantation with the most common indication being restrictive lung disease (43.1%). Nearly half of the LTR had primary systemic hypertension. Most patients (67.1%) had a sick contact prior to onset of illness. Median forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were 2305 mL and 2955 mL, respectively, prior to diagnosis of COVID-19. The median time from the date of lung transplantation to infection was 1260 days. Utilizing the statistical analyses outlined above, the relationship between these patient characteristics with hospitalization and mortality were analyzed, however no statistically significant relationships were observed.

Table 1 Demographics

Characteristics (n = 72)	Total	Hospitalized	p-value*	Mortality	p-value**
Age, median (IQR)	53.5 (41-66)	58 (46-67.5)	0.425	66 (63.5-70)	0.096
Sex, men, n (%)	45 (62.5%)	18 (40.0%)	0.571	2 (4.44%)	0.878
BMI, median (range)	26.0 (15.5-38.4)	25.5 (22.4-29.2)	0.694	25.2 (21.2-29.8)	0.865
Non-white Race, n (%)	33 (45.8%)	13 (39.4%)	0.951	1 (3.0%)	0.657
White, n (%)	39 (54.2%)				
Hispanic, n (%)	20 (27.8%)				
Black, n (%)	5 (6.9%)				
Other, n (%)	8 (11.1%)				
Sick contacts prior to COVID, n (%)	49 (67.1%)				
Transplantation type, double n (%)	56 (77.8%)	19 (33.9%)	0.166	1 (1.7%)	0.171
Co-morbidities					

Hypertension, n (%)	32 (44.4%)	13 (40.6%)	0.806	2 (6.3%)	0.843
Chronic Kidney Disease, n (%)	17 (23.6%)	7 (41.2%)	0.721	1 (6.7%)	0.586
Congestive Heart Failure, n (%)	6 (8.3%)	2 (33.3%)	0.825	1 (16.7%)	0.109
Diabetes Mellitus, n (%)	21 (29.2%)	6 (28.6%)	0.315	1 (4.8%)	0.871
Obesity n (%)	11 (15.3%)	3 (27.3%)	0.447	1 (9.1%)	0.319
Lung Disease prior to transplantation n (%)					
Restrictive Lung Disease, n (%)	31 (43.1%)				
COPD, n (%)	12 (16.7%)				
Cystic Fibrosis, n (%)	13 (18.1%)				
Pulmonary Hypertension, n (%)	16 (22.2%)				
Lung function					
FEV1 pre COVID, median (IQR) mL	2305 (1680-2805)				
FVC pre COVID, median (IQR) mL	2955(2300-3555)				
ACR Prior to COVID n (%)	16 (22.2%)	8 (50%)	0.242	1 (6.3%)	0.636
Prior CLAD n (%)	23 (31.9%)	9 (39.1%)	0.845	2 (8.7%)	0.188
Therapeutic drug level prior to COVID infection n (%)	67 (93.1%)				

Table 1 Illustrates demographic data including age, sex, race, presence of sick contacts prior to infection. It also outlines the number of patients who previously underwent double lung transplant as well as comorbidities, lung function prior to infection, rates of rejection prior to infection and whther or not the patients were at therapeutic levels of immunosuppressive drugs prior to infection. Counts are represented as a numerical value with percentages of total population in parentheses. Medians are represented with numerical values with interquartile ranges in parentheses. P-values were then calculated for outcomes of hospitalization and mortality using Chi-Square analyses for categorical variables and Mann-Whitney U tests for continuous variables. All calculations were performed using R 4.2.2. *P-values calculated for the probability of hospitalization based on the presence of the variable identified in the row. **P-values calculated for the probability of mortality based on the presence of the variable identified in the row.

3.2 Clinical Characteristics of COVID-19 and Treatment

The most common presenting symptoms were cough (47.2%), dyspnea (29.2%) and fever (23.6%). Over a quarter of patients (26.4%) were asymptomatic and were incidentally diagnosed during screening prior to procedures (Table 2). Radiographic abnormalities were noted in half of the patients (54.2%), while the remaining did not have any changes from their baseline at time of COVID-19 diagnosis. Bilateral infiltrates were seen in 23.6%, while 19.4% had ground glass opacities and 9.7% with focal consolidations. Radiographic changes were based on CT Chest findings when available (47.2% of patients), the remaining patients findings were based from chest X-Ray results. All results represent the final radiographic read from an attending radiologist. Over a third of the patients (37.5%) were admitted; including 7/27 (25.9%) requiring intensive care unit (ICU) admission

requiring 100% FiO_2 via High-Flow Nasal Canula or Mechanical Ventilation at some point during their hospitalization. One patient additionally required venovenous extracorporeal membrane oxygenation (vvECMO).

Table 2 Clinical Characteristics (n = 72).

Symptoms, n (%)	
Fever, n (%)	17 (23.6%)
Cough, n (%)	34 (47.2%)
Dyspnea, n (%)	21 (29.2%)
GI symptoms (nausea, vomiting, diarrhea, poor appetite), n (%)	7 (9.7%)
2 symptoms	23 (31.9%)
3 or more symptoms	4 (5.6%)
Asymptomatic	19 (26.4%)
Radiographic changes at diagnosis, n (%)*	
Bilateral infiltrates, n (%)	17 (23.6%)
Focal consolidation, n (%)	7 (9.7%)
Ground glass opacities, n (%)	14 (19.4%)
No change from pre COVID baseline, n %)	33 (45.8%)
Admission, n (%)	27 (37.5%)
ICU stay, n (%)	7 (9.7%)
Co-infection, n (%)	7 (9.7%)
ECMO, n (%)	1 (1.4%)

Table 2 Illustrates symptoms of infection radiographic changes after infection. It also outlines rates of hospital admission, ICU admission, bacterial coinfection, and treatments administered including medications, supportive oxygen and ECMO. Counts are represented as numerical values with percentages in parentheses. *Radiographic changes were based on CT Chest findings when available, otherwise findings were based from chest X-Ray results. All results represent the final radiographic read from an attending radiologist.

3.3 Superimposed Infections

A minority of patients (9.7%) had confirmed superimposed bacterial pneumonias: *Pseudomonas aeruginosa* (n = 4), *Staphylococcus aureus* (n = 2), *Achromobacter xylosoxidians* (n = 1). All but one patient sick enough to warrant ICU admission were treated with empiric antibiotics regardless of confirmation of superimposed bacterial infection.

3.4 Medical Management

Prior to onset of COVID-19, 73.6% patients had received at least one vaccination dose (Table 3). Of these patients, 32.1% received 1 or 2 doses, and the remaining 67.9% received 3 or 4 doses of vaccine. Of those vaccinated, 62.3% received the Elasomeran vaccine, 35.8% received the Tozinameran vaccine, and 1.9% received a combination of both vaccines. Additionally, 18.1% of patients received pre-exposure prophylactic therapy (PrEP) with Tixagevimab/cilgavimab (Table 3), all of whom had previously been vaccinated. The majority of patients had their antimetabolite

(mycophenolate mofetil or azathioprine) dose reduced (18.1%) or held (43.1%), although this was not protocolized, and was dependent on the clinical judgement of the provider. When compared to the treatment options utilized in the management of COVID-19 patients in prior viral variant eras, the COVID-19 Omicron variant era saw a rise in the prevalence of monoclonal antibody (mAb) therapies including Casirivimab/Imdevimab, Bebtelovimab and Sotrovimab. Overall, our population of LTRs saw 59.7% treated monoclonal antibody (mAb) therapy. In addition to mAb therapy, 15.3% were treated with intravenous dexamethasone, and 26.4% received Remdesivir. At 93.1%, the vast majority of patients had therapeutic immunosuppression levels at time of diagnosis (Table 4). In general, the use of Remdesivir was recommended in patients hospitalized for COVID-19 without contraindications for the medication, and steroids were recommended in patients suffering from hypoxic respiratory failure due to COVID-19, but ultimately their use was dependent on clinical judgement of the provider.

Table 3 Vaccination and Pre-infection Prophylaxis (n = 72).

Vaccination	
Any dose of vaccine, n (% of total)	53 (73.6%)
Elasomeran, n (% of vaccinated)	33 (62.3%)
Tozinameran, n (% of vaccinated)	19 (35.8%)
Elasomeran and Tozinameran, n (% of vaccinated)	1 (1.9%)
Vaccinated x1-2, n (% of vaccinated)	17 (32.1%)
Vaccinated x3-4, n (% of vaccinated)	36 (67.9%)
PrEP	
Tixagevimab/cilgavimab, n (%)	13 (18.1%)

Table 3 Illustrates rates of pre-infection vaccination, separated by each vaccine type, and number of total doses administered. Also outlines rates of pre-infection prophylaxis with Tixagevimab/cilgavimab. Counts are represented as numerical values with percentages in parentheses.

Table 4 Treatments (n = 72).

Treatment	
Need for supplemental O2 (%)	12 (16.7%)
Need for mechanical ventilation	5 (6.9%)
Antiproliferative agent reduced, n (%)	13 (18.1%)
Antiproliferative agent held, n (%)	31 (43.1%)
Steroids, n (%)	11 (15.3%)
Remdesivir, n (%)	19 (26.4%)
Monoclonal Antibody Therapy, n (%)	43 (59.7%)
Casirivimab/Imdevimab, n (%)	10 (13.9%)
Bebtelovimab, n (%)	18 (25%)
Sotrovimab, n (%)	15 (20.8%)

Table 4 Illustrates the breakdown of treatments administered, with further characterization of each monoclonal antibody therapy given. Counts are represented as numerical values with percentages in parentheses.

3.5 Outcomes and Survival

Of the total population, 84.7% (72 LTR) underwent follow up spirometry 1-2 months after infection. The median drop in FEV1 and FVC within 1-2 months after COVID-19 infection was 140 mL and 25 mL, respectively. This represented a drop in percentage of predicted FEV1 of 4.84% and in FEV1 of 0.64%. Those with the largest drop in FVC and FEV1 were patients who were either found to have new bilateral infiltrates on chest imaging, or those requiring admission to ICU. 70.8% of patients completed follow up spirometry at 3 months post-infection. Median reduction in FVC was slightly larger at 75 ml, while median FEV1 measurements dropped by only 55 ml. This correlated with a drop in percentage of predicted FEV1 of 2.69% and in FVC of 3.03%. Notably, only the drop in FEV1 at 3 months was found to be statistically significant with a p-value of 0.022 (Table 5, Figure 1).

Table 5 Outcomes and Survival (n = 72).

Lung Function		**p-value**
FEV1 1-2mo post COVID in mL, median (IQR)	2165 (1568-2630)	
FVC 1-2mo post COVID in mL, median (IQR)	2930 (2333-3545)	
Reduction in FEV1 1-2 month post COVID in mL, median	140	0.121
Reduction in percent of predicted FEV1 1-2 month post COVID in %, median	4.84%	
Reduction in FVC 1-2 month post COVID COVID in mL, median	25	0.439
Reduction in percent of predicted FVC 1-2 month post COVID in %, median	0.64%	
FEV1 3mo post COVID in mL, median (IQR)	2250 (1630-2710)	
FVC 3mo post COVID in mL, median (IQR)	2880 (2330-3470)	
Reduction in FEV1 3 month post COVID in mL, median	55	0.022
Reduction in percent of predicted FEV1 3 month post COVID in %, median	2.69%	
Reduction in FVC 3 month post COVID in mL, median	75	0.163
Reduction in percent of predicted FVC 3 month post COVID in %, median	3.03%	
Radiographic changes > 1 month post COVID-19		
Resolving infiltrates, n (%)	18 (25.0%)	
Persistent infiltrates, n (%)	17 (23.6%)	
No change from pre COVID-19 baseline, n %)	24 (33.3%)	
ACR > 1 month Post COVID, n (%)	3 (4.2%)	
Death, n (%)	3 (4.2%)	

Table 5 Illustrates changes in lung function after infection from pre-infection baseline. Also shows radiographic changes at >1 month after infection, when compared to X Rays or CT Scans at time of infection. In addition, outlines rates of ACR >1 month after infection, as well as total

all-cause mortality. Counts are represented as a numerical value with percentages of total population in parentheses. Medians are represented with numerical values with interquartile ranges in parentheses. P-values were then calculated for changes in lung function at 1 and 3 months utilizing paired Wilcox tests. All calculations were performed using R 4.2.2.

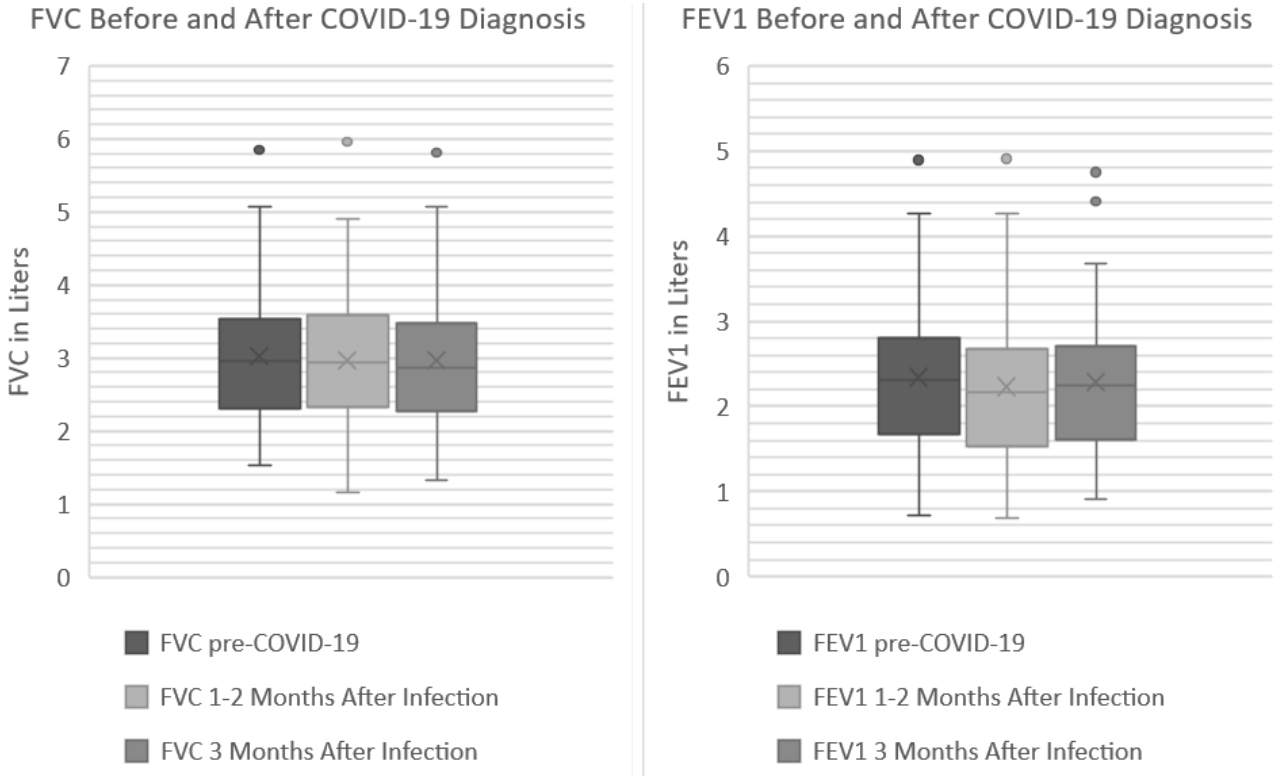

Figure 1 Changes in Spirometry.

Persistent infiltrates were found in 23.6% of patients 6 weeks after infection, and a total of 3 (4.2%) patients were definitely diagnosed with acute cellular rejection (ACR) after COVID-19 infection based on transbronchial biopsy results. One patient was diagnosed with presumptive ACR given the risk for pneumothorax was high while intubated and on mechanical ventilation after a negative bronchoalveolar lavage cultures and improvement with empiric pulse dose methylprednisolone. The other two were diagnosed with ISHLT minimal grade (A1) acute cellular rejection based on transbronchial biopsy. All three patients had therapeutic CNI levels at the time of their diagnosis of ACR.

There were three deaths during the study period due to progressive CLAD and respiratory failure. Of the three deaths, two were felt to be secondary to COVID-19 infection and occurred in patients who were on baseline supplemental oxygen with preexisting CLAD. The one remaining death was attributed to failure to thrive and worsening comorbidities, occurring over several months after resolution of COVID-19. 12 patients contracted COVID-19 within the first year post lung transplant. Of these, eight required hospitalization, with only one of these requiring ICU admission.

When considering patient symptoms, 45.3% of symptomatic patients required hospitalization, as compared to 15.8% of asymptomatic patients, reaching statistical significance (p-value 0.023). No asymptomatic patients required ICU admission, or suffered mortality, as compared to 13.2% and 5.7%, respectively, of symptomatic patients. This did not reach statistical significance (Table 6).

Table 6 Outcome Based on Presence of Symptoms.

	Asymptomatic	Symptomatic	p-value*
Hospitalized, n (%)	3 (15.8%)	24 (45.3%)	0.023
ICU admission, n (%)	0 (0%)	7 (13.2%)	0.095
Mortality, n (%)	0 (0%)	3 (5.7%)	0.289

Table 6 Illustrates the number of asymptomatic and symptomatic patients who had outcomes of hospitalization, ICU admission and mortality. Counts are represented as numerical values with percentages in parentheses. P-values were calculated for outcomes of hospitalization and mortality using Chi-Square analyses. All calculations were performed using R 4.2.2. *P-values calculated for the probability of hospitalization, ICU admission and mortality based on the presence of symptoms.

Another consideration when stratifying outcomes, is the presence of interventions such as vaccination status, PrEP and use of mAb. Looking first at vaccination status, 34% of vaccinated patients required hospitalization, while 5.7% suffered mortality, however this was not a significant impact. PrEP did result in a significantly lower rate of hospitalization at 7.7% (p-value 0.014), although despite a 0% mortality rate, this did not reach statistical significance. The most notable impact was seen from mAb therapy, which resulted in statistically significant decreases in both hospitalization at 20.9% in mAb recipients, compared to 62% in those without (p-value 0.001), as well as mortality at 0% as compared to 10.3% in those without mAb (p-value 0.031) (Table 7).

Table 7 Outcomes Based on Vaccination, PrEP and mAb.

	Hospitalized	p-value*	Mortality	p-value**
Unvaccinated, n (% of Unvaccinated)	9 (47.4%)		0 (0%)	
†Vaccinated, n (% of Vaccinated)	18 (34.0%)	0.301	3 (5.7%)	0.289
PrEP, n (% of PrEP)	1 (7.7%)	0.014	0 (0%)	0.406
mAb, n (% of mAb)	9 (20.9%)	0.001	0 (0%)	0.031

Table 7 Illustrates outcomes delineated by interventions received, including vaccination, PrEP and mAb therapy. All patients who received PrEP, also received mAb and vaccination. All patients who receive mAb also received vaccination. Counts are represented as a numerical value with percentages of population in parentheses. P-values were then calculated for outcomes of hospitalization and mortality using Chi-Square analyses. All calculations were performed using R 4.2.2. *P-values calculated for the probability of hospitalization based on the presence of the variable identified in the row. **P-values calculated for the probability of mortality based on the presence of the variable identified in the row. †Vaccinated patients include all patients who received at least 1 dose of vaccine.

As far as the use of other treatment modalities, including Remdesivir and Steroids, these were used exclusively in patients who were hospitalized, so no meaningful statistical data could be drawn from their implication on hospitalization rates. Also, all 3 patients who suffered mortality were receiving Remdesivir at the time, and 2 of them were receiving both steroids and Remdesivir. Steroids were used in 11 patients, 10 of whom also received Remdesivir. Because of this significant overlap, no statistically meaningful conclusions could be drawn from the use of these agents when

compared to each other. In addition, there was one patient who received mAb, Remdesivir and steroids, one patient who received mAb and Remdesivir, and one who received mAb and Steroids, none of whom suffered mortality. There was no other overlap in these populations. Finally, there were 12 patients who received no therapies. This population had had 0 deaths and 2 hospitalizations, however did not reach statistical significance in hospitalizations (p 0.077) or mortality (p 0.429).

3.6 COVID Variant Eras

Among the study population, 25% had COVID-19 during the "Wild Type era", 10.8% during the "Delta era", and 54.2% occurred during the "Omicron era". Of these eras, the Wild Type and Delta eras represented the highest incidence of hospitalization at 50% and 46.7%, respectively, as compared to only 28.2% hospitalization rate in the Omicron era. However, no statistically significant differences in risk for hospitalization, ICU admission or death were appreciated among the different variant eras (Table 8).

Table 8 Variant Eras (n = 72).

	Wild Type Era	Delta Era	Omicron Era	p-value
Total, n (%)	18 (25.0%)	15 (20.8%)	39 (54.2%)	
Hospitalized, n (%)	9 (50.0 %)	7 (46.7%)	11 (28.2%)	0.204
ICU Admission, n (%)	3 (16.7%)	1 (6.7%)	3 (7.7%)	0.514
Mortality, n (%)	0 (0%)	1 (6.7%)	2 (5.1%)	0.575

Table 8 Illustrates rates of hospitalization, ICU admission and mortality in each viral variant era. Counts are represented as numerical values with percentages in parentheses. P-values were calculated utilizing Chi-square analyses. All calculations were performed using R 4.2.2.

4. Discussion

Our single center observational study of LTR with COVID-19 showed low mortality rates across three viral variant eras by taking aggressive measures to modify immunosuppression and monitoring for allogenic responses. In addition to low mortality rates, our population demonstrated minimal spirometric changes at 1-2 months and at 3 months post-infection. We found that the ACR and mortality rates were significantly lower than what is reported widely in the literature [4, 21-25]. While we could not isolate any significant characteristics predictive of improved outcomes, these findings may be attributable to a combination of expedient recognition and treatment of COVID-19 as well as high rates of vaccination prior to infection [26, 27], use of prophylactic and treatment monoclonal antibody therapies, and decreasing virulence in predominant COVID-19 variants in the community at the time of this study.

Interestingly, 26.4% patients remained asymptomatic and nearly half did not have any radiographic findings associated with COVID-19 infection. Of these asymptomatic patients, 10 received 3 or more doses of vaccine, 5 had received Tixagevimab/cilgavimab and 4 patients were within 1 year of their lung transplantation. During the later pandemic, nasopharyngeal COVID PCR testing was compulsory prior to procedures, leading to the detection of many asymptomatic cases. We intentionally included these cases to help ascertain whether even asymptomatic infection may be associated with allograft dysfunction.

4.1 Hospitalization and Mortality

Our overall population demonstrated a mortality rate of only 4.2%, which remains significantly lower than the mortality rates between 8-39% currently reported in literature [5, 6, 7, 21, 25, 28]. This is despite the particularly vulnerable nature of LTR owing to increased risk of transplant rejection in the setting of viral pneumonias [15], as well as the necessity of immunosuppression and lower pulmonary reserve. In fact, in a multicenter study of solid organ transplant recipients diagnosed with COVID-19, Heldman et al found a Hazard Ratio of 1.5 in 28-day all-cause mortality in LTR compared to even other solid organ transplant recipients [29]. The most influential factor in decreasing mortality rates at our center was the administration of mAb therapy, resulting in a statistically significant drop in both hospitalization and mortality. In fact, the mortality rate decreased from 10.3% in patients who did not receive mAb, to 0% in those who did. Additionally, similar to the report from Gottlieb et al our population did not see a significant decline in mortality due to PrEP, however contrary to their results, PrEP did benefit our cohort's hospitalization rates [30]. Our low mortality rate of 4.2% may also have been influenced by a combination of multiple factors, including the evolution of the dominant strain of COVID-19 from Delta and wild-type to Omicron with a lower associated virulence, as well as earlier testing and more frequent testing of asymptomatic patients, and early mAb therapy use in our cohort. Unfortunately our population size limited any statistically significant findings in variation of mortality among variants, comorbidities or demographics.

Although most of our patients had mild COVID-19 and did not require supplemental oxygen, we still had a 37.5% admission rate. Due to reports of high mortality among LTRs early in the pandemic, our lung transplant group practiced caution and admitted most patients with positive COVID-19 tests and concerning respiratory symptoms early in the pandemic. The decision to hospitalize patients was heavily influenced by the presence of symptoms, as illustrated by a statistically significant difference in hospitalization rates of asymptomatic (15.8%) vs symptomatic patients (45.3%). While this cautious approach may have confounded the hospitalization rates, it likely improved survival outcomes.

4.2 Viral Variant Eras

Utilizing the predominating viral variant at the time of the positive viral PCR test, we differentiated patients into three variant eras: "Wild type", "Delta", and "Omicron". Among these variant eras, our study revealed that while the majority of confirmed infections occurred during the Omicron era (54.2%), there was no statistically significant difference in risk for mortality, ICU admission or hospitalization across viral variant eras.

Previous publications have shown mortality rates of 25%-34% in LTR during the wild-type and Delta variant eras [3], while Hum et al. reported a mortality rate of 12% specifically in Omicron variant era [31]. This would suggest, despite higher transmissibility in the Omicron variant widely reported in the literature, the virulence appeared lower. While this may have accounted for our lower mortality rate when compared to other studies, this subgroup analysis performed on our population did not yield any statistically significant differences in mortality.

4.3 Spirometry

Although there was a median reduction observed in both FEV1 and FVC, the only statistically significant decrease in lung function was recorded in FEV1 at three months after infection. With a median decrease of 55 mL, this decline likely signals the development of some element of airway obstruction over 3 months following the initial infection. Overall, the recorded decreases may be accounted for by the large drop in spirometry observed in patients who required ICU admission and supplemental oxygen, as well as those found to have bilateral parenchymal opacifications on imaging studies at the time of infection. By comparison, Roosma et al. found that at three months following infection, both FEV1 and FVC declined by 138 and 233 mL, respectively, and still significantly reduced at 6 months [32]. Once again, our data suggest a less detrimental post-infectious response, in line with more recently published data from Touilloux et al. [33].

4.4 Rates of Organ Transplant Rejection

Additionally our study looked at rates of ACR, which is infrequently studied or reported in other similar literature [4, 21-25]. Other respiratory viruses have shown a strong association with acute rejection, particularly RSV (75% in early RSV, 38% in late RSV) [15, 34]. Characterizing the downstream effects of COVID-19 is vital to post-transplant care as ACR is a risk factor for both chronic lung allograft dysfunction and mortality.

The incidence of ACR after COVID-19 in our cohort was very low at 4.2%, possibly explained by the small percentage of symptomatic patients who were less than 1 year post lung transplant, as these patients are at greatest risk for acute rejection. Median time after transplant for our infected patients was nearly 3.5 years.

4.5 Limitations and Future Directions

This study has several limitations. The sample size is small and involves a single center. It is also retrospective in nature, and there were a large number of asymptomatic patients included. Follow up time was limited and most patients (51/72) did not undergo bronchoscopy for surveillance of ACR and CLAD. The intermediate and long term outcomes of COVID-19 on LTR merit further investigation to optimize post-COVID-19 management in this at risk patient population.

This would benefit from further multi-center studies to delineate factors that contribute to hospitalization, mortality, ACR and CLAD. Particular attention should be paid to rates of immunization, mAb utilization, and viral variants, as these all represent understudied areas. While the future prevalence of COVID-19 is uncertain, further research in COVID-19 effects on LTR may help elucidate how to approach other Community Acquired Respiratory Virus infections.

5. Conclusions

We found a lower mortality in our single center cohort of 72 LTRs when compared to the currently available literature. We found that FEV1 and FVC volumes were also largely unchanged, and the occurrence of ACR and CLAD was rare. We attribute these favorable outcomes to the use of pre-exposure prophylactic therapy, monoclonal antibody therapy, early hospitalization and high rates of vaccination.

Nonstandard Abbreviations

LTR	Lung Transplant Recipients
ACR	Acute Cellular Rejection
CLAD	Chronic Lung Allograft Dysfunction
PCR	Polymerase Chain Reaction
CT	Computed Tomography
FEV1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
mAb	Monoclonal Antibody
vvECMO	Venovenous Extracorporeal Membrane Oxygenation

Author Contributions

A.K. and K.A. designed the study. R.G. and A.K. collected the data and wrote the manuscript. R.G. performed the statistical analysis and designed the figures and tables. All authors performed revisions and provided critical feedback in the editing of this manuscript.

Competing Interests

The authors of this manuscript have no conflicts of interest as described by the OBM Transplantation Journal.

References

1. Johns Hopkins Coronavirus Resource Center. COVID-19 Dashboard by Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) [Internet]. Washington D.C.: Johns Hopkins University & Medicine; 2023. Available from: https://coronavirus.jhu.edu/map.html.
2. Raja MA, Mendoza MA, Villavicencio A, Anjan S, Reynolds JM, Kittipibul V, et al. COVID-19 in solid organ transplant recipients: A systematic review and meta-analysis of current literature. Transplant Rev. 2021; 35: 100588.
3. Heldman MR, Kates OS, Safa K, Kotton CN, Georgia SJ, Steinbrink JM, et al. COVID-19 in hospitalized lung and non-lung solid organ transplant recipients: A comparative analysis from a multicenter study. Am J Transplant. 2021; 21: 2774-2784.
4. Saez-Giménez B, Berastegui C, Barrecheguren M, Revilla-López E, Los Arcos I, Alonso R, et al. COVID-19 in lung transplant recipients: A multicenter study. Am J Transplant. 2021; 21: 1816-1824.
5. Lawrence A, Mahan LD, Mohanka MR, Bollineni S, Kaza V, La Hoz RM, et al. Predictors and outcomes of respiratory failure among lung transplant patients with COVID-19. Clin Transplant. 2022; 36: e14540.
6. Laothamatas K, Hum J, Benvenuto L, Shah L, Grewal HS, Pereira M, et al. One year into the pandemic: Evolving COVID-19 outcomes in lung transplant recipients, a single-center experience. Transplant Direct. 2022; 8: e1296.

7. Magnusson JM, Larsson H, Alsaleh A, Ekelund J, Karason K, Schult A, et al. COVID-19 in lung transplant recipients: An overview of the Swedish national experience. Transpl Int. 2021; 34: 2597-2608.
8. Permpalung N, Bazemore K, Chiang TP, Mathew J, Barker L, Nematollahi S, et al. Impact of COVID-19 on lung allograft and clinical outcomes in lung transplant recipients: A case-control study. Transplantation. 2021; 105: 2072-2079.
9. Cozzi E, Faccioli E, Marinello S, Loy M, Congedi S, Calabrese F, et al. COVID-19 pneumonia in lung transplant recipients: Report of 2 cases. Am J Transplant. 2020; 20: 2933-2937.
10. Gergen AK, Madsen HJ, Tilva KR, Smith JB, Weyant MJ. Coronavirus disease 2019 in lung transplant recipients. Ann Thorac Surg. 2021; 111: e343-e345.
11. Antonacci F, Petroncini M, Salvaterra E, Bertoglio P, Daddi N, Lai G, et al. Lung transplant recipients and COVID-19: Report of two cases. J Clin Med. 2023; 12: 4287.
12. Donohue JK, Hyzny EJ, Clifford S, Chan EG, Coster JN, Furukawa M, et al. Immediate postoperative COVID-19 infection after lung transplantation: A systematic review and case series. J Clin Med. 2023; 12: 7028.
13. Bollineni S, Mahan LD, Duncan P, Mohanka MR, Lawrence A, Joerns J, et al. Characteristics and outcomes among vaccinated lung transplant patients with breakthrough COVID-19. Transpl Infect Dis. 2022; 24: e13784.
14. Friedman DZ, Pettit NN, MacKenzie E, Pisano J. Current and emerging therapies for COVID-19 in lung transplantation. Curr Pulmonol Rep. 2023; 12: 23-35.
15. Permpalung N, Thaniyavarn T, Saullo J, Arif S, Miller R, Reynolds J, et al. 1599. Rejection outcomes in lung transplant recipients post respiratory syncytial virus infections. Open Forum Infect Dis. 2018; 5: S501.
16. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. Am J Respir Crit Care Med. 2019; 200: e70-e88.
17. Verleden GM, Glanville AR, Lease ED, Fisher AJ, Calabrese F, Corris PA, et al. Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment-A consensus report from the pulmonary council of the ISHLT. J Heart Lung Transplant. 2019; 38: 493-503.
18. Stewart S, Fishbein MC, Snell GI, Berry GJ, Boehler A, Burke MM, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transplant. 2007; 26: 1229-1242.
19. Office of the Commissioner. FDA authorizes booster dose of Pfizer-BioNTech COVID-19 vaccine for certain populations [Internet]. Silver Spring, MD: Food and Drug Administration (FDA); 2021. Available from: https://www.fda.gov/news-events/press-announcements/fda-authorizes-booster-dose-pfizer-biontech-covid-19-vaccine-certain-populations.
20. Centers for Disease Control and Prevention. David J. Sencer CDC Museum: In association with the Smithsonian institution [Internet]. Atlanta, GA: Centers for Disease Control and Prevention; 2022. Available from: https://www.cdc.gov/museum/timeline/covid19.html.
21. Messika J, Eloy P, Roux A, Hirschi S, Nieves A, Le Pavec J, et al. COVID-19 in lung transplant recipients. Transplantation. 2021; 105: 177-186.
22. Myers CN, Scott JH, Criner GJ, Cordova FC, Mamary AJ, Marchetti N, et al. COVID-19 in lung transplant recipients. Transpl Infect Dis. 2020; 22: e13364.

23. Aversa M, Benvenuto L, Anderson M, Shah L, Robbins H, Pereira M, et al. COVID-19 in lung transplant recipients: A single center case series from New York City. Am J Transplant. 2020; 20: 3072-3080.
24. Mohanka MR, Mahan LD, Joerns J, Lawrence A, Bollineni S, Kaza V, et al. Clinical characteristics, management practices, and outcomes among lung transplant patients with COVID-19. J Heart Lung Transplant. 2021; 40: 936-947.
25. Kamp JC, Hinrichs JB, Fuge J, Ewen R, Gottlieb J. COVID-19 in lung transplant recipients-risk prediction and outcomes. PLoS One. 2021; 16: e0257807.
26. Scharringa S, Hoffman T, van Kessel DA, Rijkers GT. Vaccination and their importance for lung transplant recipients in a COVID-19 world. Expert Rev Clin Pharmacol. 2021; 14: 1413-1425.
27. Huh K, Kang M, Kim YE, Choi Y, An SJ, Seong J, et al. Risk of severe COVID-19 and protective effectiveness of vaccination among solid organ transplant recipients. J Infect Dis. 2023; jiad501. doi: 10.1093/infdis/jiad501.
28. Amor SM, Fox BD, Grubstein A, Rosengarden D, Shostak Y, Shitenberg D, et al. Poor outcomes of COVID-19 in lung transplant recipients. Cohort study in a single center. J Heart Lung Transplant. 2021; 40: S144.
29. Heldman MR, Kates OS, Rakita RM, Lease ED, Limaye AP, Fisher CE. 468. Delayed mortality among solid organ transplant recipients hospitalized for Covid-19: An international multicenter study. Open Forum Infect Dis. 2021; 8: S336-S337.
30. Gottlieb J, Simon S, Barton J, Barnikel M, Bachmann M, Klingenberg MS, et al. Efficacy of pre-exposure prophylaxis to prevent SARS-CoV-2 infection after lung transplantation: A two center cohort study during the omicron era. Infection. 2023; 51: 1481-1489.
31. Hum J, Laothamatas K, Scheffert J, Nolan M, Reilly G, D'Ovidio F, et al. Impact of omicron on lung transplant recipients: A third COVID-19 surge with different outcomes. Ann Am Thorac Soc. 2023; 20: 148-151.
32. Roosma E, Van Gemert JP, De Zwart AE, Van Leer-Buter CC, Hellemons ME, Berg E, et al. The effect of COVID-19 infection on transplant function and development of CLAD in lung transplant patients: A multicenter experience. J Heart Lung Transplant. 2022; 41: S110-S111.
33. Touilloux B, Papadimitriou-Olivgeris M, Bongard C, Mansouri N, Ioakeim F, Manuel O, et al. Impact of COVID-19 on long-term lung function in lung transplant recipients: A single-center retrospective cohort study. Transpl Infect Dis. 2023; 25: e14151.
34. Peghin M, Hirsch HH, Len Ó, Codina G, Berastegui C, Sáez B, et al. Epidemiology and immediate indirect effects of respiratory viruses in lung transplant recipients: A 5-year prospective study. Am J Transplant. 2017; 17: 1304-1312.