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Outcomes of COVID-19 in a Large Cohort of Lung Transplant Recipients: A Retrospective Study

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Abstract: *Background:* Early reports of COVID-19 in lung transplant recipients (LTRs) showed high hospitalization and mortality rates. However, the outcomes of COVID-19 in LTRs since the advent of newer therapies and vaccines have been poorly defined. *Methods:* We evaluated the risks for SARS-CoV-2-related hospitalization and mortality in a cohort of LTRs at the Henry Ford Lung Transplant Program in Detroit, Michigan during the study period March 2020–March 2022. Univariate logistic regression, followed by multivariable modeling were performed to estimate the odds ratio (OR) with 95% confident intervals (CI). *Results:* Sixty-four laboratory-confirmed SARS-CoV-2 infections were identified in 59 patients. For the primary analysis of the hospitalization and mortality risks, we included these 59 patients with symptomatic COVID-19. SARS-CoV-2 infections were confirmed with real-time polymerase chain reaction (RT-PCR) from a nasopharynx swab. The mean age (±STD) was 61 (±12), 63% were males, 27% were African Americans, and the time from lung transplant to COVID-19 was 5.5 (±4.8) years. Thirty-four (57.6%) patients were hospitalized, and the inpatient mortality rate was 24% (8/34). A multivariable analysis showed that patients with a higher baseline forced expiratory volume (FEV1) were less likely to be hospitalized (OR = 0.91 and 95% CI 0.87–0.98, $p = 0.02$). Seventy-five percent (75%; 6/8) of patients on invasive mechanical ventilation died, compared with only 8% mortality rate in those without mechanical ventilation (OR = 36.0 and 95% CI 4.2–310.4, $p < 0.01$). Although a trend toward a higher risk of death was observed in those infected during the Alpha ($p = 0.17$) and Delta ($p = 0.22$) waves, no significant risk was detected after adjusting for other covariates. Five LTRs were diagnosed with COVID-19 twice. Thirty of the sixty-four COVID-19 cases (46.8%) occurred in LTRs that had received at least two doses of any of the available mRNA vaccines at a median of 123 days (IQR 98–164 days) after vaccination. Twelve of the thirty (40%) were hospitalized, and four patients (33%) died during their hospitalizations. *Conclusions:* In our LTR population, the hospitalization and mortality rates associated with COVID-19 were high despite the increased use of new therapies. Vaccine-breakthrough infections were common and were associated with poor outcomes. Studies are needed to determine optimal prevention and therapeutic strategies to improve COVID-19 outcomes in LTRs.

Keywords: COVID-19; lung transplant recipients; immunocompromised; breakthrough infections

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1. Introduction

Few centers across the globe have reported on the outcomes of COVID-19 in lung transplant recipients (LTRs) [1–6]. Most reports relate to the early period following the declaration of the COVID-19 pandemic in March 2020 by the World Health Organization. These initial reports, predominately of hospitalized LTRs with short-term follow-ups, showed high hospitalization and mortality rates associated with COVID-19. The mortality rate of COVID-19-related acute respiratory distress syndrome (ARDS) requiring invasive

mechanical ventilation was significantly higher in LTRs than in the immunocompetent patient population (75–100% versus 20–40%, respectively) [7–9], even if compared with non-immunosuppressed patients with severe refractory hypoxic respiratory failure on venovenous extracorporeal membrane oxygenation (vvECMO). In a registry of 1900 solid organ transplant (SOT) recipients with COVID-19, including over 150 LTRs, the morbidity and mortality rates were higher for LTRs compared with other SOT recipients [10].

Since these early reports, the modalities used for the treatment and prevention of COVID-19 have rapidly evolved. Remdesivir, an antiviral agent administered to hospitalized patients with moderate illness who did not require hospitalization into an intensive care unit (ICU), was shown to shorten the time to clinical recovery [11,12]. In patients with COVID-19-related pneumonia and hypoxic respiratory failure, landmark studies of corticosteroid therapy demonstrated significant improvement in outcomes and reduced mortality [13]. Favorable outcomes were reported with the use of immunomodulators, such as tocilizumab and baricitinib, in addition to corticosteroids in patients with severe and critical COVID-19 [12,14]. The use of anticoagulation to prevent venous thromboembolism (VTE); high quality critical care, including treatment of secondary infections; the support of other organs; and the avoidance of further damage by the ventilator or self-induced lung injury are standard of care. Venous thromboembolism prevalence was found to be higher in COVID-19 patients than in other ICU patient populations [15]. In noncritically ill patients with COVID-19, an initial strategy of therapeutic-dose anticoagulation with heparin was associated with better outcomes [16]. These modalities were incorporated into guidelines endorsed by several medical societies for the treatment of COVID-19, utilizing a tiered approach based on the severity of illness [17]. Additionally, the modification of immunosuppression (corticosteroid augmentation and the discontinuation of cell-cycle inhibitors) was recommended in SOT recipients (SOTRs) [18,19].

In December 2020, messenger RNA vaccines received an Emergency Use Authorization in the United States of America. The effectiveness of these vaccines was noted to be suboptimal in SOTRs due to the immunosuppressant therapies used to prevent rejection and an attenuated immune response [20]. Vaccine effectiveness was further compromised by the emergence of variants of SARS-CoV-2 [21]. Other therapies aimed to prevent serious illness in this high-risk population became available over time, including different compositions of monoclonal antibodies and oral antivirals [22].

However, the effect of these new modalities of therapy on the outcomes of COVID-19 in the LTR population is incompletely understood. We described the clinical course and outcomes of COVID-19 in 59 LTRs, as well as the incidences of vaccine-breakthrough infections from March 2020 to March 2022 at our institution. The primary outcome of interest for our study was examining the risk of COVID-19-related hospitalization and inpatient mortality.

2. Methods

2.1. Study Design

This was a single-center retrospective cohort study that included all adult LTRs at the Henry Ford Transplant Institute, who were symptomatic and tested positive for SARS-CoV-2 with a real-time polymerase chain reaction (RT-PCR) test via a nasopharyngeal swab from March 2020 to March 2022. This study was approved by the Henry Ford Health System Institutional Review Board (#14948) and consent was waived.

2.2. Data Collection and Definitions

Patient information was obtained by review of the electronic health records (EHR). Demographics, clinical characteristics, comorbidities, date and indication of transplantation, date of COVID-19 diagnosis, disease severity, and management were evaluated. COVID-19 vaccination data were obtained from the EHR and the Michigan Care Improvement Registry (MCIR), which reports COVID-19 vaccine administration. All patients were followed until 31 March 2022.

"COVID-19 severity" was defined as per the National Institutes of Health (NIH) COVID-19 guidelines [23]. "Vaccine-breakthrough infection" was defined as having COVID-19 diagnosed at least 14 days after the administration of a COVID-19 vaccine, i.e., a minimum of 2 doses of an mRNA vaccine [21]. The periods of activity in the United States of America (USA) of the various SARS-CoV-2 variants were based on the Center for Disease Control and Prevention (CDC) timeline [23]. The approximate periods of activity for the variants were: wild-type (March 2020–December 2021); Alpha (January 2021–April 2021); Delta (May 2021–December 2021); and Omicron (January 2022 onwards).

2.3. Statistical Analysis

The patients' characteristics and clinical conditions were summarized. The mean (SD) was used for the continuous variable, and percentage was used for the categorical and binary variables for all patients. Non-normally distributed numerical variables were summarized as medians with interquartile range.

The data were compared between two groups of patients with symptomatic COVID-19 (hospitalized versus non-hospitalized) and based on the vital statuses of inpatients (dead versus alive). The chi-square test/Fisher exact test were used for categorical variables and a two-sample t-test was used for continuous variables to study the univariate effect of the variables on each outcome of interest. Stepwise logistic regression was preformatted to study the risk/association to hospitalization. Variables would retain in the model if there was a significant effect with p-value < 0.05 after adjusting for the other covariates with estimation of odds ratio (OR) and its 95% confident intervals (CI), where OR < 1 and 95% CI < = 1 indicates a proactive effect for hospitalization, while OR > 1 and 95% CI > 1 indicates a risk for hospitalization. A similar analysis was performed to study the risk/association to inpatient death.

The statistical analysis was performed with SPSS version 25.0 (IBM Corp, Armonk, NY, USA).

2.4. COVID-19 Management

The decision to hospitalize LTRs and the level of care needed were made by the lung transplant team based on disease severity. In general, LTRs were hospitalized if they had hypoxia or severe symptoms (tachypnea with a respiratory rate of >30 breaths/minute, chest pain, dyspnea, etc.) suggestive of a progression to respiratory failure and clinical instability. The standard of care of hospitalized COVID-19-infected LTRs was based on the disease stage and severity, using institutional protocols that were consistent with NIH treatment guidelines [17]. Patients with mild or moderate disease and unchanged baseline oxygenation were treated as outpatients. The general recommendation was symptomatic treatment, to isolate, hydrate well, and communicate with the LT coordinators if symptoms worsened. Immunosuppression management changed over the course of the pandemic, with a discontinuation of the cycle-cell inhibitors in all LTRs with any severity of COVID-19 during the Delta variant period, and in hospitalized LTRs regardless of the circulating variant at the time of a COVID-19 diagnosis. In patients with mild and moderate COVID-19 that were not hospitalized, a virtual visit was conducted 1 week after the diagnosis of COVID-19 to confirm clinical improvement or the need of hospitalization in case of disease progression. At follow-up visits, the decision to resume the cell-cycle inhibitor was made on average 31 days after discontinuation in 9 patients who did not require hospitalization. Additional therapy with monoclonal antibodies was utilized as they became available in outpatients to prevent disease progression.

For hospitalized patients with mild-to-moderate COVID-19, the administration of intravenous remdesivir was considered within 7 days of symptom onset. In patients with COVID-19-related pneumonia and hypoxia, the corticosteroid dose was increased. In addition, for patients in the ICU with high levels of inflammatory markers and oxygen therapy requiring non-invasive or invasive mechanical support, tocilizumab or baricitinib were considered on a case-by-case basis.

3. Results

3.1. Patient Characteristics, Clinical Course, and Management

A query of all 170 LTRs routinely followed-up with our program identified 59 LTRs with symptomatic COVID-19 from March 2020 to March 2022: a cumulative incidence of 34.7%. Five LTRs were diagnosed with SARS-CoV-2 twice and their disease severities varied, with only one patient hospitalized twice during each COVID-19 diagnosis. The most common symptoms of COVID-19 at presentation were dyspnea, nausea, vomiting, fever, diarrhea, and cough. A CT scan of the chest was available in 27 of 34 (79%) cases of hospitalized patients. Bilateral ground-glass opacities (GGO) were present in 70% of cases, and single-lung GGO was present in 30%. The time from the COVID-19 diagnosis to CT chest scan was a median of 2 days (IQR 0–11 days).

Sixty-four laboratory-confirmed SARS-CoV-2 infections were identified in these 59 patients, of whom 34 (57.6%) were hospitalized. Most patients in this cohort underwent bilateral LT for idiopathic interstitial pneumonia (38%) or chronic obstructive pulmonary disease (20.6%). Other indications included fibrotic interstitial lung disease associated with connective tissue diseases, sarcoidosis, pulmonary artery hypertension, cystic fibrosis, and e-cigarette- or vaping-use-associated lung injury (in one patient, the first case ever described of LT for this indication in the USA [24]). Three patients underwent dual organ transplants with bilateral LT (one heart–lung and two liver–lung), and another patient underwent redo bilateral LT for advanced bronchiolitis obliterans syndrome.

The baseline characteristics of thirty-four hospitalized and twenty-five non-hospitalized patients are summarized in Table 1. The median age at diagnosis was 64 years, 62% were males, 66% Caucasians, and 27% were African Americans. The two groups were generally comparable, except hospitalized patients were more likely to be women and African Americans. The median FEV1 (mL) prior to COVID-19 was lower in hospitalized patients at 1675 (IQR 1440–2100) compared with 2400 (IQR 1620–2790) in non-hospitalized patients ($p = 0.01$) (Supplementary Materials).

The maintenance immunosuppression regimen for most LTRs consisted of a combination of corticosteroids and a calcineurin inhibitor. A cell-cycle inhibitor was part of the regimen in 47% and rapamycin in 13% of patients at baseline. Most patients (77%) were receiving azithromycin for bronchiolitis obliterans syndrome prophylaxis. The mean time post-LT to COVID-19 diagnosis was 5.4 years ($\pm$4.8). No cases were reported in newly transplanted patients (<6 months post-LT). All cases were acquired through community exposure to cases of COVID-19 within their households. The largest number of COVID-19 cases occurred during the period of Delta variant activity (19 patients; 10 LTRs required hospitalization). Monoclonal antibodies (casirivimab-imdevimab, bamlanivimab-etesivimab, and bebtelovimab or sotrovimab), based on CDC recommendations, were administered to 14 patients at the outpatient setting. Two of them required hospitalization and there were no deaths.

Of the 34 LTRs with COVID-19 that were hospitalized for hypoxic respiratory failure secondary to SARS-CoV-2 infection, one patient was hospitalized twice for separate infection episodes.

The standard of care of hospitalized COVID-19-infected LTRs was based on institutional protocols. Frequently used therapies in our hospital include augmented corticosteroids, remdesivir, tocilizumab or baricitinib, supplemental oxygen, anticoagulation, and supportive care, as clinically indicated. Intravenous remdesivir was only administered to hospitalized patients (55%, 19/34), and IV tocilizumab was administered in four cases of critical COVID-19 without contraindications (two patients in the ICU did not receive IV tocilizumab due to an active infection). Baricitinib was used in only one patient.

Table 1. Baseline characteristics of hospitalized and non-hospitalized lung transplant recipients with COVID-19.

Variable	*Response*	*All N = 59*	*Non-Hospitalized N = 25*	*Hospitalized N = 34*	† *p-Value*
Gender	F	22 (37%)	6 (27%)	16 (73%)	0.07
	M	37 (63%)	19 (51%)	18 (49%)	
Age	Mean ± SD	61.42 ± 12.27	61.48 ± 9.77	61.38 ± 13.97	0.98
Race	African American	16 (27%)	3 (19%)	13 (81%)	0.04
	Caucasian	39 (66%)	21 (54%)	18 (46%)	
	Others	4 (7%)	1 (25%)	3 (75%)	
BMI	Mean ± SD	28.25 ± 7.74	27.89 ± 6.13	28.52 ± 8.82	0.76
Reason for LT					0.31
	Idiopathic interstitial pneumonia	23 (39%)	10 (43%)	13 (57%)	
	COPD	12 (20%)	6 (50%)	6 (50%)	
	Other fibrotic ILD	8 (14%)	3 (38%)	5 (63%)	
	Sarcoidosis	8 (14%)	1 (13%)	7 (88%)	
	PAH	3 (5%)	1 (33%)	2 (67%)	
	Cystic fibrosis	2 (3%)	2 (100%)	0 (0%)	
	EVALI	1 (2%)	0 (0%)	1 (100%)	
	Re-Do Transplant	1 (2%)	1 (100%)	0 (0%)	
LT type	Bilateral Lung	52 (88%)	23 (44%)	29 (56%)	0.72
	Single Lung	4 (7%)	1 (25%)	3 (75%)	
	Liver/Lung	2 (3%)	1 (50%)	1 (50%)	
	Heart/Lung	1 (2%)	0 (0%)	1 (100%)	
Post Op Month	Mean ± SD	65.76 ± 57.96	53.92 ± 41.98	74.47 ± 66.61	0.15
FEV1_mL	Mean ± SD	2031.86 ± 835.91	2352.40 ± 935.51	1796.18 ± 675.67	0.01
CLAD	None	30 (51%)	18 (60%)	12 (40%)	0.08
	BOS Stage 1	9 (15%)	2 (22%)	7 (78%)	
	BOS Stage 2	11 (19%)	2 (18%)	9 (82%)	
	BOS Stage 3	6 (10%)	4 (67%)	2 (33%)	
	RAS	3 (5%)	1 (33%)	2 (67%)	
Comorbidities					0.33
	HTN	35 (60%)	16 (46%)	19 (54%)	
	DM	28 (48%)	12 (43%)	16 (57%)	
	BMI > 30	19 (32%)	7 (37%)	12 (63%)	
	CKD 3 or higher	39 (66%)	16 (41%)	23 (29%)	

LT, lung transplant; BOS, bronchiolitis obliterans syndrome; CKD, chronic kidney disease; CLAD, chronic allograft dysfunction following the International Society for Heart and Lung Transplantation 2002 classification; COPD, chronic obstructive pulmonary disease; EVALI, e-cigarette- or vaping-use-associated lung injury; ILD, interstitial lung disease; IQR, interquartile range; LTRs, lung transplant recipients; PAH, pulmonary artery hypertension, RAS, restrictive allograft syndrome. One patient had typical clinical and radiological features of COVID-19 with a negative RT-PCR test, but subsequently developed positive SARS-CoV2 antibodies. † $p < 0.05$ significant.

An ICU level of care was necessary in 14 LTRs (14/59, 24%), and eight of these patients (8/14, 57%) required invasive mechanical ventilation for severe hypoxemia. No LTRs received extracorporeal membrane oxygenation support. Cell-cycle inhibitors were discontinued in all cases of LTRs requiring hospitalization.

3.2. Vaccine Breakthrough

Vaccination with a minimum of two doses of a COVID-19 mRNA vaccine (BNT162b2 or Pfizer-BioNTech, and mRNA-1273 or Moderna) were recommended for all our LTRs. Fifty patients in this cohort completed a two-shot vaccination series (Pfizer: 33 patients; Moderna: 17 patients), and nine patients were unvaccinated at the time of the data censoring. COVID-19 occurred in 30 patients who received at least a two-doses series of an mRNA vaccine at a median of 123 days (IQR 98–164 days) after vaccination. Twelve of the thirty patients (40%) were hospitalized and four of these patients died (overall mortality: 13.3%; inpatient mortality: 33%). The three patients that required invasive mechanical ventilation died. Of

the 50 vaccinated patients, 31 received a third dose. Of the 31 patients that received a third dose, 19 had breakthrough infections (61.2%), and two patients died.

3.3. Outcomes

The patients were followed for a median of 150 days (IQR 68–369). The result of the multivariable analysis showed that patients with a higher baseline forced expiratory volume (FEV1) were 9% less likely to be hospitalized (OR = 0.91 and 95% CI 0.87–0.98, $p = 0.02$). The overall mortality was 13% (8/59), with an inpatient mortality of 23.5% (8/34), and 75% of those mechanically ventilated died (6/8). The mortality rate was 8% (28/34) in patients hospitalized without treatment with mechanical ventilation (OR = 36.0 and 95% CI 4.2–310.4, $p < 0.01$). Of the eight patients that died during the study period, four were patients with vaccine-breakthrough COVID-19. The cause of death in seven patients was septic shock and multiorgan failure. One patient died from antibody-mediated rejection 2 months following a COVID-19 infection. Common critical COVID-19 complications were sepsis, invasive mechanical ventilation, and acute kidney injury (Acute Kidney Injury Network stage 3). Bacterial and mold infections were commonly identified.

The characteristics of patients that died and those who survived are shown in Table 2. The patient demographics; underlying comorbidities; time from LT, FEV1, and CLAD; and presumed type of variant were comparable in both groups. Most deaths (four patients) occurred during the period of Delta variant activity. Although there was a trend of lower mortality observed during the Alpha wave (9%), and a higher mortality rate during the Delta wave (36%), no significant risk was detected after adjusting for the other covariates.

Table 2. Factors associated with mortality among hospitalized patients.

Variable	*Response*	*Hospitalized N = 34*	*Dead N = 8*	*Alive N = 26*	*p-Value*
Gender	F	16 (47%)	4 (25%)	12 (75%)	0.85
	M	18 (53%)	4 (22%)	14 (78%)	
Age	Mean ± SD	61.38 ± 13.97	66.63 ± 8.78	59.77 ± 14.99	0.23
Race	African American	13 (38%)	3 (23%)	10 (77%)	0.91
	Caucasian	18 (53%)	4 (22%)	14 (78%)	
	Others	3 (9%)	1 (33%)	2 (67%)	
BMI	Mean ± SD	28.52 ± 8.82	31.09 ± 9.67	27.74 ± 8.58	0.35
Reason for LT	IIP	13 (38%)	4 (31%)	9 (69%)	0.85
	EVALI	1 (3%)	0 (0%)	1 (100%)	
	Other fibrotic ILD	5 (15%)	1 (20%)	4 (80%)	
	COPD	6 (18%)	2 (33%)	4 (67%)	
	Sarcoidosis	7 (21%)	1 (14%)	6 (86%)	
	PAH	2 (6%)	0 (0%)	2 (100%)	
LT type	Bilateral Lung	29 (85%)	7 (24%)	22 (76%)	0.85
	Single Lung	3 (9%)	1 (33%)	2 (67%)	
	Liver/Lung	1 (3%)	0 (0%)	1 (100%)	
	Heart/Lung	1 (3%)	0 (0%)	1 (4%)	
Post Op Month	Mean ± SD	74.47 ± 66.61	74.75 ± 42.78	74.38 ± 73.11	0.99
FEV1_mL	Mean ± SD	1796.18 ± 675.67	1761.25 ± 455.02	1806.92 ± 737.66	0.87
CLAD					0.63
	BOS Stage 1	7 (21%)	2 (29%)	5 (71%)	
	BOS Stage 2	9 (26%)	2 (22%)	7 (78%)	
	BOS stage 3	4 (12%)	0 (0%)	4 (100%)	
	RAS	2 (6%)	0 (0%)	2 (100%)	

Table 2. *Cont.*

Variable	*Response*	*Hospitalized N = 34*	*Dead N = 8*	*Alive N = 26*	*p-Value*
Comorbidities					0.33
	HTN	3 (9%)	1 (33%)	2 (67%)	
	DM	2 (6%)	0 (0%)	2 (100%)	
	BMI > 30	3 (9%)	2 (67%)	1 (33%)	
	CKD 3 or higher	24 (71%)	5 (21%)	19 (79%)	
Medical ward		20 (59%)	0 (0%)	20 (100%)	<0.01
ICU		14 (41%)	8 (57%)	6 (43%)	<0.01
IMV		8 (24%)	6 (75%)	2 (25%)	<0.01
SARS-CoV-2 wave					
First_wave		10 (29%)	2 (20%)	8 (80%)	0.75
Alpha_wave		11 (32%)	1 (9%)	10 (91%)	0.17
Delta_wave		11 (32%)	4 (36%)	7 (64%)	0.22
Omicron_wave		4 (12%)	1 (25%)	3 (75%)	0.94
Breakthrough	N = 30	12 (40%)	4 (33%)	9 (75%)	0.43

BMI, body mass index; IIP, idiopathic interstitial pneumonia; PAH, pulmonary arterial hypertension; BOS, bronchiolitis obliterans syndrome; CKD, chronic kidney disease; CLAD, chronic allograft dysfunction following the International Society for Heart and Lung Transplantation 2002 classification; FEV1, forced expiratory volume in 1 s; IMV, invasive mechanical ventilation; RAS, restrictive allograft syndrome; SD, standard deviation.

4. Discussion

In this retrospective case study of 59 LTRs with symptomatic SARS-CoV-2 infections, we noted a high overall mortality rate of 13%, an inpatient mortality of 24%, and a 75% mortality rate in those mechanically ventilated.

A higher FEV1 at baseline was found to be protective against hospitalization with an OR = 0.91 (95% CI 0.87–0.98, $p = 0.02$). The risk for severe COVID-19 and a high mortality rate in LTRs have been demonstrated in previous reports [25–28]. A study across 68 ICUs in different regions of the United States found a 28-day ICU mortality of 40% in severe COVID-19 cases in 98 SOTRs (including four LTRs) [26]. In a registry from the University of Washington of 1900 SOT cases, including over 150 LTRs with at least 28-days follow-up after SOT, the mortality rate was 15% regardless of the season (these data were collected from the spring to fall of 2020). Over a third of hospitalized patients required an ICU level of care [10]. In the largest single-center study to date that included 32 LTR patients with severe COVID-19, the reported overall mortality rate was 47% (with a 100% mortality rate in those requiring invasive mechanical ventilation) [1]. In a study of 11 LTRs hospitalized for COVID-19, the ICU admission rate was 45%, and the mortality rate was 71% in those requiring mechanical ventilation [5].

All deaths in our study occurred in hospitalized LTRs with severe or critical COVID-19. Of the eight patients that died, COVID-19 was the cause of death in seven of the patients, and one patient died from antibody-mediated rejection two months following the COVID-19 infection. Six of the eight patients on invasive mechanical ventilation died. No deaths were identified in non-hospitalized LTRs with mild or moderate COVID-19 symptoms. Although the immunosuppression in LTRs may play a role, the key determinants of severity and mortality in SARS-CoV-2-infected LTRs are advanced age and underlying comorbidities. The comorbidities frequently seen in LTRs are arterial hypertension, renal failure, and cardiovascular diseases, which are also risk factors for adverse outcomes in COVID-19 in the general population.

Although our mortality rate was consistent with previous reports, our cohort had a larger proportion of African Americans (27%) compared with that in other studies. Previous reports suggested that the African American population is more severely affected by COVID-19, which was attributed to a higher prevalence of underlying comorbidities, as well as social inequalities resulting in less access to the health care system, especially at the beginning of the pandemic [29]. Most COVID-19 cases and deaths occurred during the

period of Delta variant activity, and generally paralleled the patterns of COVID-19 reported in the state of Michigan.

Furthermore, our report highlighted the risk of vaccine-breakthrough infections (30/64, 46.8% of the described cases) and the risk of COVID-19-related hospitalization and death, even in LTRs with a series of two doses of a COVID-19 vaccine. The hospitalization and mortality rates in our 30 LTRs with vaccine-breakthrough infections were 40% (12/30) and 13% (4/30), respectively. In comparison, a recent study of breakthrough COVID-19 infections in 14 LTRs that received two doses of an mRNA vaccine reported an 85.7% hospitalization and a 0% mortality rate at 4 weeks [28]. The favorable outcomes reported in that study may be a consequence of a younger cohort of patients (median age: 54 years) and milder disease at the time of hospitalization, as only 50% of the patients had clinical features of lower respiratory tract infection. Moreover, breakthrough COVID-19 infections in our cohort occurred at a median of 123 days post-vaccination when the vaccine-induced immunity is expected to wane. COVID-19 vaccination is an important strategy in preventing severe disease, hospitalization, and death; however, immune responses to vaccination are impaired in LTRs [20]. Less than a quarter of LTRs developed protective levels of antibodies after two or three doses of mRNA vaccines in studies that measured IgG antibody titers against domains of the SARS-CoV-2 spike protein to assess the serological response [30–33]. Similarly, cell-mediated immune responses are suboptimal in LTRs [34]. Factors that affect poor immune responses in LTRs include the use of cell-cycle inhibitors, such as mycophenolic acid; old age; induction therapy; and a regimen combination of tacrolimus plus mycophenolic acid with/without steroids [35]. The type of vaccine and optimal number of COVID-19 mRNA vaccine doses still need to be determined [20]. Most guidelines currently recommend four doses of an mRNA vaccine for transplant recipients, as well as the vaccination of close contacts [36,37].

The limitations of this study included its retrospective design, single-center data, absence of the genotyping of variants, and lack of autopsies to support cause of death. However, the study had several strengths including the large number of LTRs with COVID-19 diagnosed during the early and late periods of the pandemic when more modalities of therapy became available. In addition, the study described one of the largest cohorts of LTRs with vaccine-breakthrough infections.

5. Conclusions

We confirmed and expanded on the results from previous studies of COVID-19 infections in LTRs. The mortality from COVID-19 remained high in the LTR population despite the use of newer modalities of therapy. A higher FEV1 at baseline with a difference of at least 100 mL was shown to protect against hospitalization. Breakthrough COVID-19 infections are common in vaccinated LTRs and can result in severe disease. Additional studies are needed to determine the optimal vaccination strategies in the LTR population. Risk mitigation strategies including social distancing and masking during periods of high transmission, and prompt diagnosis and treatment are important. The long-term effects of COVID-19 on lung allografts remain unknown.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/transplantology3030026/s1, Table S1: Baseline characteristics of lung transplant recipients with COVID-19 based on level of care; Table S2: Characteristics of 59 lung transplant recipients with symptomatic COVID-19.

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