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A Single-center Experience With >200 Lung Transplant Recipients With COVID-19 Infection

Hiromu Kehara, MD, PhD,[1] Ashley Johnson-Whiting, NP-C,[1] Roh Yanagida, MD, PhD,[1] Kewal Krishan, MD,[1] Huaqing Zhao, PhD,[2] Aaron Mishkin, MD,[3] Francis Cordova, MD,[4] Gerard J. Criner, MD,[4] Yoshiya Toyoda, MD, PhD,[1] and Norihisa Shigemura, MD, PhD[1,4]

Background. Although COVID-19 is no longer a declared global health emergency, data remain limited on the impact of COVID-19 in lung transplant recipients. **Methods.** We identified lung transplant recipients who were diagnosed with COVID-19 from March 2020 through August 2022 in our institutional database and investigated clinical outcomes. We then analyzed outcomes based on date of COVID-19 diagnosis (first wave March 2020–October 2020; second wave November 2020–2021; third wave December 2021–September 2022) and compared these results. **Results.** Of the 210 lung transplant recipients (median age 67; 67% men) enrolled, 140 (67%) required hospital admission. Among admitted recipients, 35 (25%) were intubated and 7 (5%) were placed on extracorporeal membrane oxygenation. Overall survival was 67.1% at 1 y and 59.0% at 2 y post-COVID-19 diagnosis. COVID-19 led to mortality in all 5 patients diagnosed during their index admission for lung transplantation. Although overall survival was significantly better in recipients with COVID-19 during the third wave, in-hospital mortality remained high (first wave 28%, second wave 38%, and 28% third wave). Vaccination (partially vaccinated versus none and fully vaccinated versus none) was the only significant protective factor for hospital admission, and age 70 y and older and partially vaccinated (versus none or fully vaccinated) were independent risk factors for in-hospital mortality. **Conclusions.** Overall survival after COVID-19 infection in lung transplant recipients continues to improve; however, in-hospital mortality remains remarkably high. Vaccination appears to have been impactful in preventing hospital admission, but its impact on in-hospital mortality is still unclear. Further research is needed to better identify lung transplant recipients at high risk for mortality from COVID-19.

(*Transplantation Direct* 2024;10: e1676; doi: 10.1097/TXD.0000000000001676.)

Although case numbers and death rates associated with the SARS-CoV-2/COVID-19 pandemic are declining and the end of COVID-19 as a global health emergency has been declared, the assessment of its impact in many fields of medicine remains to be completed. Analysis is particularly important in the field of lung transplantation because a new COVID-19 variant or another virus affecting the respiratory system could precipitate another pandemic.

COVID-19 had a huge impact on the organ transplant community. The number of organ transplants performed has significantly decreased all over the world since early 2020.[1] Moreover, COVID-19 can be life-threatening to organ transplant recipients because of their coexisting medical comorbidities and need for immunosuppression. Although treatment options, including vaccines and antiviral therapeutics, continue to evolve, the virus itself has also been changing (eg, the emergence of

Received 19 March 2024. Revision received 22 April 2024.

Accepted 15 May 2024.

[1] Division of Cardiovascular Surgery, Lewis Katz School of Medicine at Temple University, Philadelphia, PA.

[2] Department of Biomedical Education and Data Science, Center for Biostatistics and Epidemiology, Lewis Katz School of Medicine at Temple University, Philadelphia, PA.

[3] Section of Infectious Diseases, Department of Medicine, Lewis Katz School of Medicine at Temple University, Philadelphia, PA.

[4] Department of Thoracic Medicine and Surgery, Temple University Hospital, Philadelphia, PA.

The authors declare no funding or conflicts of interest.

H.K. participated in study design, data collection and analysis, and writing the article. A.J.-W. participated in data collection. R.Y., K.K., A.M., F.C., G.J.C., and Y.T. participated in critical revision. H.Z. participated in data analysis. N.S. participated in study design, writing the article, and critical revision.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

Correspondence: Norihisa Shigemura, MD, PhD, Division of Cardiovascular Surgery, Lewis Katz School of Medicine at Temple University, 3401 N Broad St, Zone C, 3rd Floor, Suite 301, Philadelphia, PA 19140; Department of Cardiothoracic Surgery, University of Pittsburgh School of Medicine, 200 Lothrop St, C-920, Pittsburgh, PA 15213. (shigemuran3@upmc.edu).

This article was presented at the oral session of the 43rd annual meeting and scientific session of The International Society for Heart and Lung Transplantation, Denver, CO, April 19 to 22, 2023.

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001676

the Delta and Omicron variants), resulting in a waning effect from vaccines.[2] Outcomes after COVID-19 infection in organ transplant recipients have been increasingly reported (**Table S1, SDC,** http://links.lww.com/TXD/A676),[3-10] but data specific to lung transplant recipients remain sparse.[11,12]

Our high-volume lung transplant center is located in a geographical area with a persistently high COVID-19 infection rate. We have been trying to continue lung transplantation with extremely cautious steps, including dual COVID-19 screening through reverse transcription polymerase chain reaction testing and high-resolution CT chest imaging because lung transplantation is a life-saving procedure.[13] We also have cared for many patients infected with COVID-19 after lung transplantation as well as patients who developed acute respiratory distress syndrome and progressive post-COVID-19 pulmonary fibrosis as a result of COVID-19, some of whom then required a lung transplant. Our multidisciplinary team approach to COVID-19 has included screening, diagnosis, and management of patients and has been consistently used during the course of the pandemic.[13-17] In this study, we analyzed outcomes after COVID-19 infection in lung transplant recipients using our large institutional data set and compared the outcomes during 3 time periods characterized by different circulating virus variants to evaluate our institutional approach to these enduring challenges.

MATERIALS AND METHODS

Study Design

Of the 1040 patients who received a lung transplant at Temple University Hospital (TUH) from 2012 through September 2022, lung transplant recipients who were diagnosed with COVID-19 between March 26, 2020, and September 6, 2022, were identified for inclusion in this study. Additionally, 342 patients who received a lung transplant at TUH from January 1, 2020, to September 6, 2022, were identified to compare the survival of lung transplant recipients diagnosed with COVID-19 with recipients without a COVID-19 diagnosis.

We reviewed medical charts to identify patient characteristics, treatments for COVID-19, and early outcomes. Survival after COVID-19 infection was determined from clinical records. The last follow-up date was September 14, 2022. We investigated the prevalence and clinical outcomes of the entire cohort and then divided the cohort into 3 groups depending on the date of COVID-19 diagnosis based on well-characterized waves of the COVID-19 pandemic (first wave: March 26, 2020, to October 31, 2020, second wave: November 1, 2020, to November 30, 2021, and third wave: December 1, 2021, to September 6, 2022). Patients were considered COVID-19-positive based on polymerase chain reaction testing or on the consensus opinion of the multidisciplinary team that included surgeons, pulmonologists, and infectious disease specialists after considering chest computed tomography (CT) findings and clinical presentation. The CT findings were also compared between single lung transplant (SLT) and double lung transplant (DLT) recipients.

This study was approved by the Temple University Institutional Review Board (protocol No. 30385). The requirement for the patient's informed consent was waived because of the minimal risk posed by the study.

Vaccination

Patients were classified as "partially vaccinated" after the second dose of the BNT162b2 (Pfizer) or mRNA-1273 (Moderna) vaccines or after 1 dose of the JNJ-78436735 (Johnson & Johnson) vaccine. They were classified as "fully vaccinated" if they received any subsequent doses of any COVID-19 vaccine.

Vaccination was strongly advised to lung transplant recipients after it became available. Vaccination also became mandatory for the patients to be listed as lung transplant candidates in April 2021.

COVID-19 Treatment

The criteria for hospital admission have been described in detail elsewhere.[5] The patients requiring hospital admission received COVID-19 treatment at an outside institution or TUH. Regarding immunosuppressive medications during treatment for COVID-19, calcineurin inhibitors were continued, mycophenolate was held, and steroids were augmented on the basis of the patient's clinical status. When possible, efforts were made to enroll patients in clinical trials for COVID-19 treatments, including remdesivir and convalescent plasma. Each patient's treatment was determined by the multidisciplinary team. Tixagevimab and cilgavimab were used routinely beginning in late 2021.

Statistical Analysis

Continuous variables are shown as median with interquartile range. Categorical variables are shown as absolute numbers with percentages. The Mann-Whitney *U* test was used for comparison of continuous variables, and Pearson's χ^2 test or Fisher exact test was used for comparison of categorical variables between the 3 groups. Overall survival and conditional survival were estimated using the Kaplan-Meier method and compared using the log-rank test. Survival probability with 95% confidence intervals is shown. Risk factors for hospital admission and hospital mortality were assessed using univariate and multivariable logistic regression models. Variables with a *P* value of <0.10 in univariate analysis were incorporated into the multivariable logistic regression models. A *P* value of <0.05 was considered significant. All statistical analyses were conducted with JMP Pro 15 software (SAS Institute, Cary, NC).

RESULTS

Study Population

In total, 210 lung transplant recipients with a COVID-19 diagnosis were assessed in this study. Patient demographics are shown in Table 1. Their median age was 67 y, and 79 (38%) were older than 70 y (Table 1). SLT was performed in 147 of the patients (70%), and DLT was performed in 63 (30%). The median time from lung transplant to COVID-19 diagnosis was 2.1 y. Five patients were diagnosed with COVID-19 during their index admission for lung transplantation.

When the lung transplant recipients were divided into 3 groups based on the date of COVID diagnosis: 35 contracted COVID during the first wave of the pandemic (16.7%), 69 had COVID illness during the second wave (32.9%), and half (n = 106; 50.5%) had COVID during the third wave of the pandemic (Figure 1). The patients in the first wave were diagnosed with COVID-19 significantly sooner after lung

TABLE 1.

Patient demographics

Variable	Total (N = 210)	First (N = 35)	Second (N = 69)	Third (N = 106)	*P*
Age, y	67 (61–73)	65 (59–72)	67 (63–73)	67 (61–73)	0.293
≥70	79 (38%)	12 (34%)	26 (38%)	41 (39%)	0.897
Male	141 (67%)	27 (77%)	44 (64%)	70 (66%)	0.368
Race					0.312
White	153 (73%)	27 (77%)	50 (72%)	76 (72%)	
Black	34 (16%)	5 (14%)	14 (20%)	15 (14%)	
Asian	10 (5%)	3 (9%)	1 (1%)	6 (6%)	
Other	13 (6%)	0 (0%)	4 (6%)	9 (8%)	
Transplant indication					0.120
Pulmonary fibrosis	122 (58%)	15 (43%)	45 (65%)	62 (58%)	
Chronic obstructive pulmonary disease	66 (31%)	17 (49%)	19 (28%)	30 (28%)	
Chronic lung allograft dysfunction	7 (3%)	1 (3%)	0 (0%)	6 (6%)	
Other	15 (7%)	2 (6%)	5 (7%)	8 (8%)	
Transplant type					0.053
Single lung transplantation	147 (70.0%)	20 (57%)	54 (78%)	73 (69%)	
Double lung transplantation	63 (30.0%)	15 (43%)	15 (22%)	33 (31%)	
Body mass index,[a] kg/m^2	28.0 (24.0–31.0)	23.5 (20.8–28.5)	29.0 (25.5–32.0)	28.0 (24.8–32.3)	0.005
Coronary artery disease	23 (11%)	3 (9%)	10 (14%)	10 (9%)	0.512
Baseline creatinine,[a] mg/dL	1.62 (1.36–2.19)	1.43 (0.86–2.00)	1.74 (1.49–2.36)	1.60 (1.35–2.27)	0.022
Hemoglobin A1c,[a] %	6.0 (5.6–6.8)	5.9 (5.3–6.2)	6.2 (5.6–6.8)	6.0 (5.7–6.8)	0.185
Baseline O_2 requirement[a]	9 (6%)	3 (9%)	2 (4%)	4 (8%)	0.507
Baseline forced expiratory volume in 1 s,[a] L	1.79 (1.24–2.35)	1.88 (1.24–2.68)	1.89 (1.33–2.32)	1.56 (1.08–2.34)	0.284
Years since transplant	2.1 (0.9–3.6)	0.5 (0.1–1.9)	2.2 (1.0–3.6)	2.4 (1.0–4.0)	<0.001
Index admission	5 (2%)	4 (11%)	0 (0%)	1 (1%)	<0.001
Within 1 y	54 (26%)	18 (51%)	13 (19%)	23 (22%)	<0.001
Vaccination status					<0.001
None	89 (42%)	35 (100%)	41 (59%)	9 (8%)	
Partially vaccinated	58 (28%)	0 (0%)	20 (29%)	40 (38%)	
Fully vaccinated	63 (30%)	0 (0%)	8 (12%)	57 (54%)	
Recurrent COVID infection	24 (11%)	5 (14%)	7 (10%)	12 (11%)	0.821
Readmission prior 1–3 mo[a]	24 (17%)	6 (19%)	9 (16%)	9 (17%)	0.949
6-mo survival	71.2%	68.5%	62.3%	78.9%	

Continuous variables are shown as median (interquartile range). Categorical variables are shown as absolute numbers (percentages).
[a]Only admission patients (n = 140).

transplant than patients diagnosed with COVID-19 during the second and third waves (0.5 versus 2.2 versus 2.4 y, $P < 0.001$), including 18 patients (51%) who were diagnosed with COVID-19 within 1 y after lung transplant.

At the time of their COVID-19 diagnosis, 89 patients (42%) were unvaccinated and 121 patients (58%) were vaccinated, including 63 patients (30%) fully vaccinated (Table 1). More patients were vaccinated over time; nonetheless, there were still 9 patients (8%) diagnosed with during the third wave who were not vaccinated at the time of their COVID-19 diagnosis.

Hospital Treatment and Early Outcomes

Two-thirds of the lung transplant recipients with COVID-19 illness (n = 140; 67%) required hospital admission, including 46 (33%) who required an intensive care unit (ICU) stay. Among patients admitted to the ICU, 35 (25%) were intubated, 7 (5%) required hemodialysis, and 7 (5%) were placed on venovenous extracorporeal membrane oxygenation. Characteristics of hospitalized patients are summarized in Table 2. Of the 140 lung transplant recipients admitted for COVID-19 infection, 44 died while hospitalized (mortality rate of 31%). The cause of death was attributed to COVID-19 in 35 patients and manifested as acute respiratory failure (n = 8), multiorgan failure (n = 10), or a superimposed infection (n = 17; **Table S2, SDC,** http://links.lww.com/TXD/A676). All 5 patients diagnosed with COVID-19 during their index admission for lung transplant died during this admission.

The need for hospitalization among lung transplant recipients with COVID-19 decreased as the pandemic progressed; 32 (91%) required hospitalization during the first wave, 56 (81%) during the second wave, and 52 (49%) during the third wave ($P < 0.001$). Whereas pulse-dose steroids were used more frequently for treatment during the first wave, remdesivir and baricitinib were used more frequently during the second and third waves (Table 2). The number of lung transplant recipients who required ICU admission and mechanical ventilation decreased during the third wave, but this difference was not significant. Although the length of hospital stay was significantly shorter for lung transplant recipients who contracted COVID-19 during the second or third wave, in-hospital mortality did not change over time (first wave: 28%, second wave: 38%, and third wave: 28%).

Factors Associated With Hospital Admission and In-hospital Mortality

Vaccination was the only significant protective factor for hospital admission (partially vaccinated versus none: odds ratio [OR] 0.24; fully vaccinated versus none: OR 0.30;

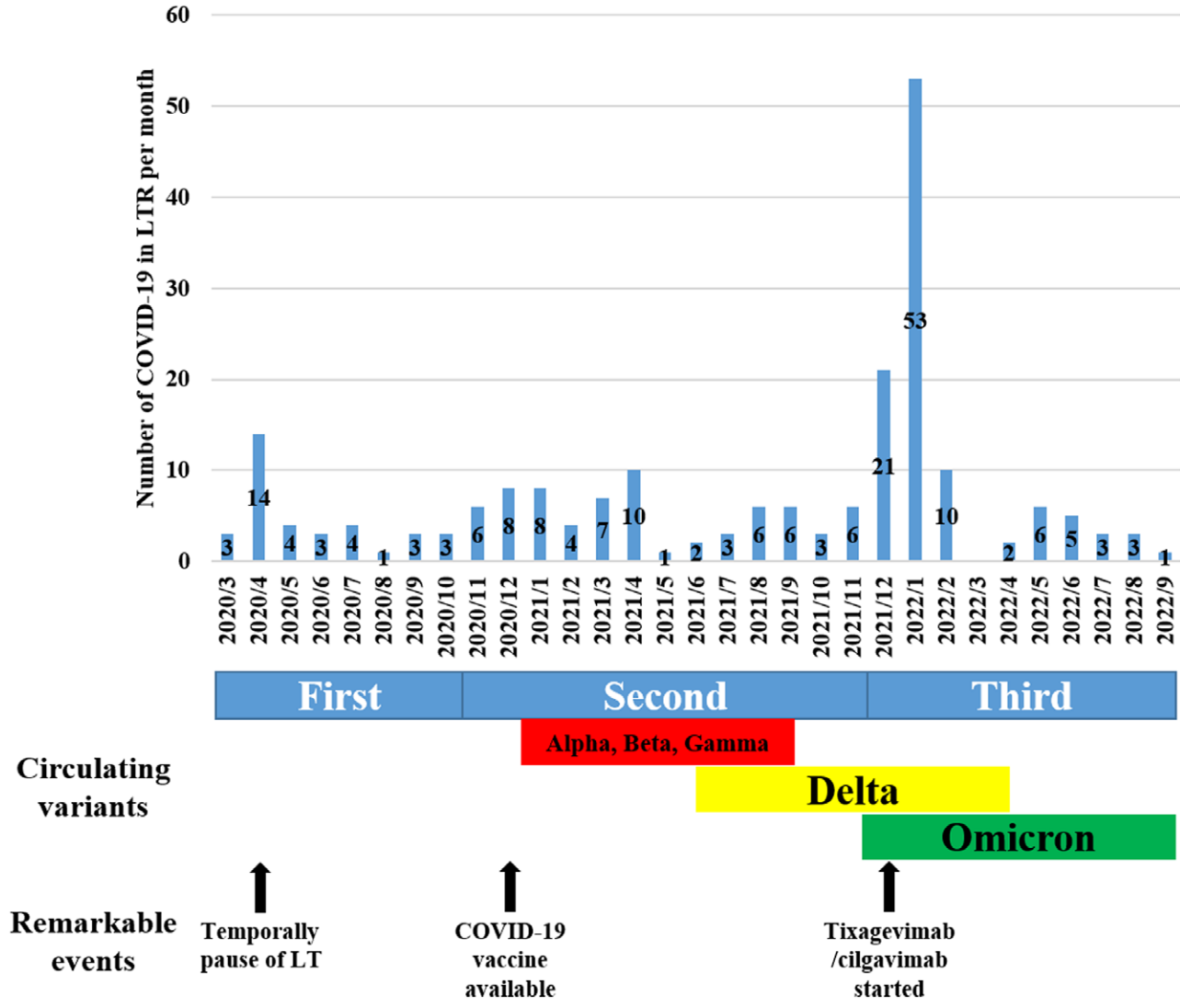

FIGURE 1. Number of monthly COVID-19 infections in LTRs divided into 3 waves. LT, lung transplantation; LTR, lung transplant recipient.

Table 3). Age 70 y and older (OR 2.96) and partially vaccinated (versus none: OR 2.60; versus fully vaccinated: OR 3.41) were independent risk factors for in-hospital mortality (Table 4).

Overall Survival

During a median follow-up of 245 d (range, 0–892), overall survival for all lung transplant recipients in our cohort was 67.1% ± 3.5% at 1 y and 59.0% ± 4.4% at 2 y post-COVID-19 infection (Figure 2A). Survival conditional on hospital discharge after COVID-19 infection was 86.1% ± 3.3% at 1 y and 75.7% ± 4.9% at 2 y (**Figure S1, SDC,** http://links.lww.com/TXD/A676). Survival was significantly better in lung transplant recipients who contracted COVID-19 during the third wave ($P = 0.017$; Figure 2B) compared with those with COVID-19 during the first or second wave.

To better understand the impact of COVID-19 on lung transplant surgery during the pandemic, we performed subgroup analysis. Between January 1, 2020, and September 6, 2022, 342 lung transplants were performed at TUH, and 71 of these recipients (21%) subsequently became infected with COVID-19. In recipients who contracted COVID-19, overall survival was 87.0% ± 4.0% at 1 y and 76.6% ± 5.4% at 2 y after lung transplant in patients with COVID-19. In the 271 transplant recipients who did not develop COVID-19, overall survival was 91.3% ± 1.9% at 1 y and 80.3 ± 3.6% at 2 y. There was no significant difference between these 2 groups ($P = 0.425$; **Figure S2, SDC,** http://links.lww.com/TXD/A676). Pulmonary function test was obtained for hospitalized patients who survived COVID-19 (n = 71). Pre-COVID-19 and post-COVID-19 forced expiratory volume in 1 s were 1.83 and 1.56 L, respectively (median interval was 18 mo, $P = 0.002$). One patient (0.5%) required a redo lung transplant after COVID-19 infection.[17]

CT Findings

Chest CT was obtained in 101 patients (48%), including 30 DLT recipients and 71 SLT recipients (Table 5). Most of DLT recipients (n = 22; 73%) had ground glass opacity (GGO) findings bilaterally. In SLT patients, GGO was observed bilaterally in 16 patients (23%), unilaterally in the allograft in 40 patients (56%), and unilaterally in the native lung in 5 patients (7%). Thus, in SLT recipients, GGO was found on CT in 79% of allografts (n = 56) and 30% of the

TABLE 2.

Characteristics of hospitalized patients

Variable	Total (N = 140)	First (N = 32)	Second (N = 56)	Third (N = 52)	Recent (N = 24)[a]	P
Baseline characteristics						
Race						0.332
White	96 (68%)	24 (75%)	40 (72%)	32 (61%)		
Black	28 (20%)	5 (16%)	12 (21%)	11 (21%)		
Asian	8 (6%)	3 (9%)	1 (2%)	4 (8%)		
Other	8 (6%)	0 (0%)	3 (5%)	5 (10%)		
Clinical presentation						
Duration of symptoms before admission, d	2 (1–5)	2 (1–3)	2 (0.5–5)	2.5 (0–5.3)		0.771
4C score at the time of admission	11 (9–14)	11 (8–13)	12 (10–14)	13 (9–15)		0.077
SOFA score at the time of admission	3 (2–4)	3 (2–4)	3 (2–4)	4 (2–5)		0.211
C-reactive protein, peak, mg/dL	10.2 (4.9–16.2)	11.4 (8.7–15.6)	10.4 (3.2–18.8)	8.7 (3.3–14.1)		0.258
Ferritin, peak, ng/mL	494 (230–1274)	696 (206–3812)	563 (286–1162)	403 (211–826)		0.501
D-dimer, peak, g/mL	1994 (978–6406)	4421 (1043–6431)	3120 (1125–7410)	1260 (903–4896)		0.163
Treatment						
Medication						
Steroid	84 (60%)	17 (53%)	38 (68%)	29 (56%)		0.293
Pulse dose	16 (11%)	13 (41%)	3 (5%)	0 (0%)		<0.001
Remdesivir	87 (62%)	10 (31%)	42 (75%)	35 (67%)		<0.001
Anakinra	16 (11%)	3 (9%)	5 (9%)	8 (15%)		0.527
Baricitinib	17 (12%)	0 (0%)	12 (21%)	5 (10%)		0.010
Tocilizumab	36 (26%)	5 (16%)	16 (29%)	15 (29%)		0.331
Intravenous immunoglobulin	25 (18%)	9 (28%)	8 (14%)	8 (15%)		0.223
Convalescent plasma	9 (6%)	3 (9%)	6 (11%)	0 (0%)		0.057
Intensive care unit treatment	46 (33%)	11 (34%)	24 (43%)	11 (21%)		0.052
Highest oxygen requirement						0.093
Mechanical ventilation	35 (25%)	9 (28%)	17 (30%)	9 (17%)		
High flow nasal cannula	11 (8%)	6 (19%)	1 (2%)	4 (8%)		
Noninvasive ventilation	4 (3%)	0 (0%)	3 (5%)	1 (2%)		
Non-rebreather	1 (0.7%)	0 (0%)	1 (2%)	0 (0%)		
Nasal cannula	40 (29%)	10 (31%)	15 (27%)	15 (29%)		
Room air	47 (34%)	7 (22%)	19 (34%)	21 (40%)		
Unknown	2 (1%)	0 (0%)	0 (0%)	2 (4%)		
Hemodialysis	7 (5%)	3 (9%)	1 (2%)	3 (6%)		0.276
Extracorporeal membrane oxygenation	7 (5%)	4 (13%)	2 (4%)	1 (2%)		0.079
Outcomes						
Hospital mortality	44 (31%)	9 (28%)	21 (38%)	14 (28%)	0 (0%)	0.461
Length of hospital stay, d	7 (5–14)	12 (6–23)	8 (4–13)	7 (5–9)	4 (3–16)	0.022
O_2 requirement on discharge	25 (18%)	11 (34%)	5 (9%)	9 (17%)		0.011

Continuous variables are shown as median (interquartile range). Categorical variables are shown as absolute numbers (percentages).
[a]Between September 7, 2022, and September 1, 2023, at least 24 patients were confirmed as COVID-19 positive. These data are not included in statistical analysis.
4C score, coronavirus clinical characterization consortium score; SOFA, sequential organ failure assessment.

native lungs (n = 21; **Figure S3, SDC,** http://links.lww.com/TXD/A676).

Chest CT was also classified into 3 categories: category 1 (consistent with multifocal pneumonia including viral/atypical pneumonia, n = 66), category 2 (indeterminate, n = 19), and category 3 (consistent with other diagnoses, n = 16; Table 5).[18]

DISCUSSION

This study of 210 lung transplant recipients who were diagnosed with COVID-19 revealed that, although the overall survival of these patients improved significantly as the pandemic progressed and treatments evolved, in-hospital mortality did not change. Although vaccination appears to have been impactful in preventing hospital admission, vaccination demonstrated inconsistent results in reducing mortality in lung transplant recipients who required hospital admission because of COVID-19 infection. To our knowledge, this is the largest single-center experience reported to date.

Persistently High In-hospital Mortality in Lung Transplant Recipients

Treatment options for COVID-19 continue to evolve, and recent studies have demonstrated significantly decreased mortality of patients with COVID-19.[19] Similar to our findings, other centers have also reported improved survival rates during the course of the pandemic in lung transplant recipients, who are thought to be particularly vulnerable to COVID-19 infection because of intense immunosuppression and the fact that the virus directly infects the transplanted organ and affects its function.[11] The group at Columbia University Medical Center reported their outcomes with

TABLE 3.

Factors associated with hospital admission

	Single variable analysis	
	OR (95% CI)	*P*
Age ≥70 y	1.50 (0.82-2.75)	0.192
Male	1.00 (0.54-1.84)	1.000
SLT (vs DLT)	1.25 (0.67-2.33)	0.474
Years since transplant	0.91 (0.81-1.03)	0.140
Within 1 y	1.60 (0.80-3.19)	0.183
Vaccination status		
Partially vaccinated vs none	0.24 (0.12-0.52)	<0.001
Fully vaccinated vs none	0.30 (0.14-0.63)	0.002
Partially vaccinated vs fully vaccinated	0.81 (0.40-1.65)	0.564
Recurrent COVID-19 infection	2.04 (0.73-5.72)	0.175
Coronary artery disease	1.47 (0.55-3.92)	0.437

CI, confidence interval; DLT, double lung transplantation; OR, odds ratio; SLT, single lung transplantation.

a 2-y follow-up recently and observed decreased mortality, hospitalizations, and severity of COVID illness in the third wave of the pandemic compared with the first and second waves, which they attributed to less virulence of the Omicron variant and improved treatment options including vaccines and remdesivir.[11,20,21] Our current study agrees with the findings of the Columbia group, and overall mortality as a result of COVID-19 in lung transplant recipients decreased. However, when a lung transplant recipient was sick enough to be admitted as a result of COVID-19 illness, in-hospital mortality was still as high at ~30%. Notably, at our center, all lung transplant recipients with COVID-19 during their index hospital admission for lung transplant died, despite the most recent patient being infected in 2022. Our study suggests that even if patients are vaccinated, mortality from COVID-19 remains extremely high in lung transplant recipients if the patient requires hospitalization. Encouragingly, however, preliminary data from our most recently treated lung transplant recipients alluded to improved clinical outcomes (**Table S3, SDC,** http://links.lww.com/TXD/A676).

Vaccinations in Lung Transplant Recipients

Conflicting results have been reported regarding serologic response and clinical effectiveness of vaccines in solid organ transplant recipients.[12,22-24] In our study, vaccination appeared to have been impactful in preventing hospital admission but demonstrated inconsistent results for reducing in-hospital mortality. Although this finding requires additional and further follow-up, we interpret that during the pandemic, vaccination was helpful but not sufficiently robust to prevent the infected patients from progressing to death unless they were fully immunized. Research has been ongoing to understand the effects of vaccinations on organ transplant recipients taking immunosuppressants. Because immunosuppression, especially with antiproliferative drugs, has been associated with poor antibody response after vaccination, recent studies have demonstrated the efficacy of a temporary reduction of immunosuppression in the weeks before and after vaccination.[25,26] However, data regarding the development of antibody-mediated rejection or chronic lung allograft dysfunction (CLAD) using this strategy are lacking. Despite negative seroconversion, a positive cellular (T cell) response has been reported.[27] Further information regarding not only humoral but also cellular responses to vaccines, along with the clinical significance of this divergence, is needed in lung transplant recipients to develop an optimal vaccine strategy.

COVID-19 in SLT Recipients

DLT is currently the preferred approach for lung transplantation nationwide, but because we have approximately

TABLE 4.

Factors associated with in-hospital mortality

	Single variable analysis		Multivariable analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age ≥70 y	2.76 (1.32-5.78)	0.007	2.96 (1.29-6.77)	0.010
Male	1.65 (0.74-3.69)	0.222		
SLT (vs DLT)	2.70 (1.08-6.74)	0.034	1.79 (0.66-4.81)	0.250
Years since transplant	1.05 (0.88-1.25)	0.589		
Within 1 y	0.65 (0.28-1.49)	0.308		
Vaccination status				
Partially vaccinated vs none	2.47 (1.02-5.95)	0.044	2.60 (1.02-6.61)	0.044
Fully vaccinated vs none	0.97 (0.40-2.39)	0.955	0.76 (0.29-2.00)	0.581
Partially vaccinated vs fully vaccinated	2.53 (0.92-6.96)	0.072	3.41 (1.14-10.20)	0.028
Recurrent COVID-19 infection	0.52 (0.16-1.67)	0.272		
Readmission prior 1–3 mo	1.66 (0.67-4.11)	0.273		
Baseline O_2 requirement	1.06 (0.25-4.45)	0.936		
Baseline FEV_1, per L	1.13 (0.61-2.08)	0.698		
Body mass index, per kg/m^2	1.01 (0.94-1.08)	0.872		
Coronary artery disease	0.49 (0.13-1.85)	0.295		
Baseline creatinine, per mg/dL	1.20 (0.94-1.53)	0.151		
Hemoglobin A1c, per %	1.20 (0.80-1.81)	0.379		
Steroid	1.34 (0.63-2.82)	0.448		
Remdesivir	1.22 (0.58-2.58)	0.602		

CI, confidence interval; DLT, double lung transplantation; FEV_1, forced expiratory volume in 1 s; OR, odds ratio; SLT, single lung transplantation.

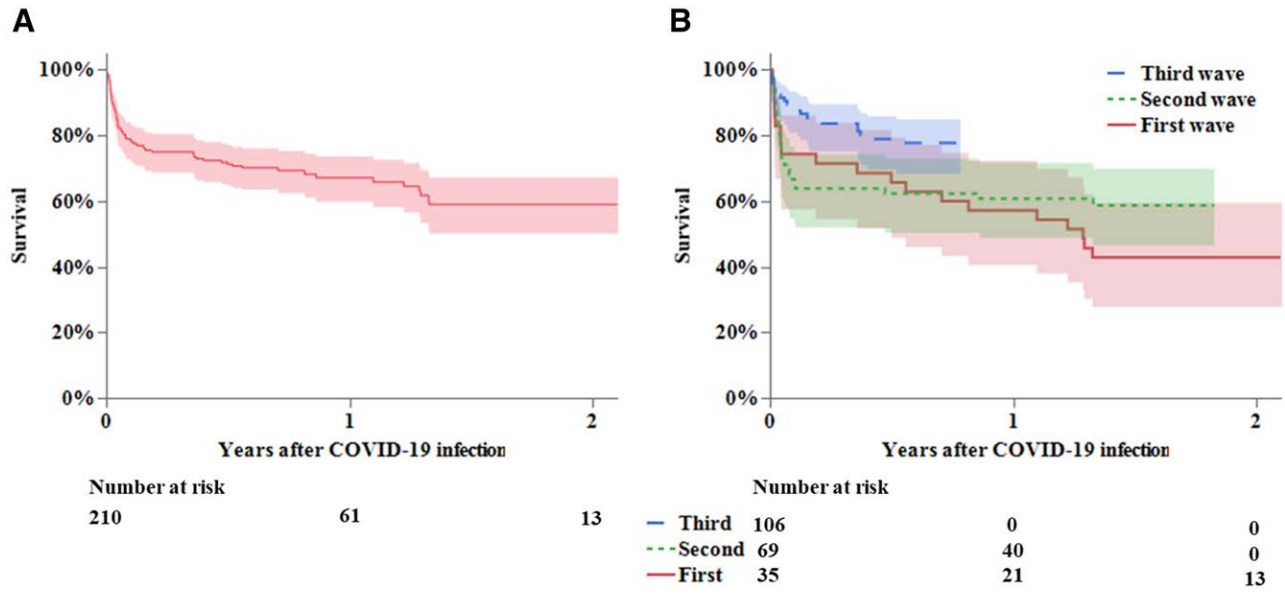

FIGURE 2. Survival after COVID-19 infection in lung transplant recipients. A, Overall survival in all patients. Overall survival was 67.1% ± 3.5% at 1 y and 59.0% ± 4.4% at 2 y post-COVID-19 infection. B, Overall survival stratified by the 3 temporal waves of the COVID-19 global pandemic. Survival was significantly better during the third wave ($P = 0.017$). Shading indicates 95% confidence intervals.

TABLE 5.

CT findings with ground glass opacity

CT findings	N = 101
Double lung transplant recipients, N = 30	
Bilateral	22 (73%)
Unilateral	4 (13%)
None	4 (13%)
Single lung transplant recipients, N = 71	
Bilateral (allograft and native lung)	16 (23%)
Unilateral (allograft)	40 (56%)
Unilateral (native lung)	5 (7%)
None	10 (14%)
Trinary read for suspected airborne infection[a]	
Category 1	66 (65%)
Category 2	19 (19%)
Category 3	16 (16%)

[a]Category 1: consistent with multifocal pneumonia including viral/atypical pneumonia. Category 2: indeterminate. Category 3: consistent with other diagnosis.
CT, computed tomography.

3 times more patients older than 70 y on our transplant waitlist proportional to our yearly lung transplant volume than on all other center waitlists in the United States,[28] approximately half of our patients undergo SLT to minimize their surgical burden. This is unique to our center. Infectious complications in SLT recipients have been described, and it has been reported that allografts tend to be infected more frequently than native lungs because of disrupted lymphatic and neural connections.[29] Our results support this with 79% of SLT recipients exhibiting GGO CT findings in their allograft compared with 30% in the native lung. Because a significant loss of lung function and new onset of CLAD were observed in lung transplant recipients who survived COVID-19,[30] further studies are warranted regarding the development of CLAD after COVID-19 infection specifically in SLT recipients compared with DLT recipients. Although our univariate analysis identified SLT as a risk factor for in-hospital mortality from COVID-19, after matching other factors, such as age, SLT was not an independent risk factor for in-hospital mortality, which is concordant with another report.[31]

The Pandemic Crisis and Its Enduring Impacts on Lung Transplantation, in Light of Pandemic History

Although overall mortality from COVID-19 in lung transplant recipients has been improving during the last 2 y, we wonder what lies ahead for the survivors. Within 2 decades, there have been 4 pandemics caused by respiratory viruses—SARS-CoV, influenza H1N1, Middle East respiratory syndrome-CoV, and SARS-CoV2 (COVID-19; Table 6). SARS-CoV and Middle East respiratory syndrome-CoV belong to the same coronavirus family as SARS-CoV2 and have high mortality rates of 9.1% and 36%, respectively;[32,33] however, likely because of the fact the outbreaks did not spread worldwide, there are few data on the effects of these viruses specifically in organ transplant recipients. In contrast, influenza H1N1 caused 151 700–575 400 deaths worldwide,[34] and there have been several reports on outcomes after influenza H1N1 in lung transplant recipients.[35-37] An Australian group reported mortality of 21% and worsening bronchiolitis obliterans syndrome grade among lung transplant recipients infected with influenza H1N1.[37] One might predict a subsequent demand for redo lung transplantation as a result; however, no cases were reported in the decade that followed. Carefully planned prospective studies should be conducted to assess the impact of COVID-19 on redo lung transplantation. One lung transplant recipient in our patient cohort underwent retransplantation, and we do not know whether more redo transplants will become necessary. Lessons and experiences from the COVID-19 pandemic are invaluable to the lung transplant community, and this experience must be carried forward to provide the best care during this enduring pandemic and during possible future pandemics.

TABLE 6.

Summary of respiratory virus pandemics

	SARS-CoV	Influenza H1N1	MERS-CoV	SARS-CoV-2 (COVID-19)
Year of the first reported case	2003	2009	2012	2019
Country of the first case	China	Mexico	Saudi Arabia	China
Deaths/total number of cases (fatality rate)	774/~8000 (9.1%)	151 700–575 400 deaths (0.02%)	935/2600 (36%)	6.64M/644M[a] (1%)
Deaths/total number of cases in the United States	0/8	12 469/60.8M	0/2	1M/98M[a]
The availability of vaccine	No	Yes	No	Currently, yes
Early outcomes in LTR	NA	Mortality 0%–21%	NA	Mortality 20%–40%
Mid- and long-term outcomes in LTR	NA	NA	NA	?

[a]As of December 1, 2022.
LTR, lung transplant recipient; M, million; MERS, Middle East respiratory syndrome; NA, not applicable.

Limitations

The present study has several limitations. First, this was a single-center, retrospective observational study, which confers an inherent selection bias. The duration of follow-up in the patients infected with COVID-19 during the third wave was short. Second, although our multidisciplinary team approach to treating COVID-19 and its sequelae has been consistent during the course of the pandemic, treatment options, including vaccines and antiviral treatments, have evolved during the last 2 y. Third, while this study was the largest single-center study to date, our cohort included patients treated both at home and in the hospital, which may make the interpretation of data somewhat demanding.

CONCLUSIONS

Overall survival post-COVID-19 infection in lung transplant recipients continues to improve; however, in-hospital mortality remains remarkably high in these patients. Whereas vaccination appeared to have been impactful in preventing hospital admission, the relationship between vaccination and in-hospital mortality was complex in our cohort. Further research focused on how to identify, monitor, and care for lung transplant recipients at high risk for mortality after COVID-19 infection is warranted and is being continued by our group.

ACKNOWLEDGMENTS

The authors thank Shannon Wyszomierski for editing a draft of the article.

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