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Pre-exposure Prophylaxis with Tixagevimab-cilgavimab did not Reduce Severity of COVID-19 in Lung Transplant Recipients with Breakthrough Infection

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Background. Lung transplant recipients (LTRs) have an increased risk of COVID-19–related morbidity and mortality. Tixagevimab-cilgavimab (tix-cil) is a long-acting monoclonal antibody combination granted Emergency Use Authorization approval by the US Food and Drug Administration for COVID-19 pre-exposure prophylaxis (PrEP) in immunocompromised patients. We sought to determine whether tix-cil 300–300 mg reduced the incidence and disease severity of severe acute respiratory syndrome coronavirus 2 infection in LTRs during the Omicron wave. **Methods.** We performed a retrospective, single-center cohort study of LTRs who had received a COVID-19 diagnosis between December 2021 and August 2022. We compared baseline characteristics and clinical outcomes after COVID-19 between LTRs who received tix-cil PrEP and those who did not. We then conducted propensity-score matching based on baseline characteristics and therapeutic interventions and compared clinical outcomes between the 2 groups. **Results.** Of 203 LTRs who received tix-cil PrEP and 343 who did not, 24 (11.8%) and 57 (16.6%), respectively, developed symptomatic COVID-19 (hazard ratio [HR], 0.669; 95% confidence interval [CI], 0.415-1.079; $P = 0.099$). The hospitalization rate of LTRs with COVID-19 during the Omicron wave trended lower in the tix-cil group than in the non–tix-cil group (20.8% versus 43.1%; HR, 0.430; 95% CI, 0.165-1.118; $P = 0.083$). In propensity-matched analyses, 17 LTRs who received tix-cil and 17 LTRs who did not had similar rates of hospitalization (HR, 0.468; 95% CI, 0.156-1.402; $P = 0.175$), intensive care unit admission (HR, 3.096; 95% CI, 0.322-29.771; $P = 0.328$), mechanical ventilation (HR, 1.958; 95% CI, 0.177-21.596; $P = 0.583$), and survival (HR, 1.015; 95% CI, 0.143-7.209; $P = 0.988$). COVID-19–related mortality was high in both propensity-score–matched groups (11.8%). **Conclusions.** Breakthrough COVID-19 was common among LTRs despite tix-cil PrEP, possibly due to reduced efficacy of monoclonal antibodies against the Omicron variant. Tix-cil PrEP may reduce the incidence of COVID-19 in LTRs, but it did not reduce disease severity during the Omicron wave. (Transplantation Direct 2023;9: e1485; doi: 10.1097/TXD.0000000000001485.)

Received 20 January 2023. Revision received 6 March 2023.

Accepted 22 March 2023.

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The authors declare no funding or conflicts of interest.

D.S., D.R., A.O., R.W., and S.T. made substantial contributions to the conception and design of the work, drafting the work or revising it critically for important intellectual content, and final approval of the version to be published, in accordance with ICMJE guidelines. D.S., D.R., K.G., L.C., and S.T. worked on the acquisition of the data, D.S. contributed to analysis, and S.T. and D.S. interpreted the data for the work. All authors agree to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001485

Infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting COVID-19 have led to significant morbidity and mortality among solid organ transplant recipients since the start of the pandemic.[1] Mutations in the viral spike protein have led to the emergence of numerous variants, with the Omicron variant and its sublineages dominating since December 2021.[2,3] Although the rates of hospitalization and in-hospital mortality fell in the general population during the Omicron surge, the morbidity and mortality among solid organ transplant recipients remained disproportionately high.[4,5]

Vaccination is the cornerstone of prevention of severe COVID-19 in the general population; however, the immune response to vaccination among solid organ transplant recipients is often inadequate, leaving them susceptible to severe illness. A study of 658 solid organ transplant recipients, including 71 lung transplant recipients (LTRs), showed that only 39% of LTRs developed an antibody response after 2 doses of a SARS-CoV-2 mRNA vaccine.[6] Furthermore, although a third vaccine dose improved the humoral response

among weak responders, the proportion of solid organ transplant recipients with no antibody response remained high.[7,8]

Neutralizing monoclonal antibodies targeting the receptor-binding domain of the SARS-CoV-2 spike protein have been isolated from COVID-19 convalescent individuals and demonstrated efficacy in preventing or treating disease in humans.[9,10] AstraZeneca's AZD7442 is a combination of 2 long-acting neutralizing monoclonal antibodies, tixagevimab and cilgavimab (tix-cil), directed against SARS-CoV-2.[9] Tixagevimab and cilgavimab bind to distinct epitopes on the SARS-CoV-2 spike protein receptor-binding domain and block its interaction with human ACE2 receptors, thereby preventing viral attachment to the cell surface. The US Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) for tix-cil in December 2021 for pre-exposure prophylaxis (PrEP) among adults and children aged 12 y or older with moderate-to-severe immune compromise.[11,12] The EUA was subsequently revised with a recommendation to double the dose of tix-cil (from 150–150 mg to 300–300 mg) based on in vitro neutralization susceptibility data.[9,13,14]

The landmark PROVENT trial randomized 5197 participants to receive tix-cil or placebo; tix-cil reduced the risk of contracting SARS-CoV-2 by 77% and also reduced disease severity among those who developed a breakthrough infection.[15] However, the trial was conducted while the Alpha and Delta variants were predominant, and later data showed reduced neutralizing antibody titers targeting the Omicron variant among tix-cil recipients, suggesting lower efficacy.[9,14] Furthermore, only 172 patients (3.3%) enrolled in PROVENT were receiving immunosuppressive therapy: 109 were treated with tix-cil and 63 with a placebo. SARS-CoV-2 breakthrough infection was rare in both groups, with 1 patient in the tix-cil group and 2 patients in the placebo group developing COVID-19. Thus, additional data are needed to illustrate the risk of breakthrough COVID-19 after tix-cil administration among patients receiving immunosuppressive therapy, such as solid organ recipients, and to characterize COVID-19 disease severity. At our large lung transplant center, we noted a high rate of breakthrough COVID-19 among LTRs who received PrEP with tix-cil during the Omicron wave, between December 2021 and August 2022. Thus, we sought to determine whether tix-cil PrEP reduced the incidence of COVID-19 or impacted the course of illness in LTRs.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective, single-center cohort study of LTRs with COVID-19 between December 2021 and August 2022, during which time the Omicron variant was predominant. Per our institutional protocol and the FDA's EUA, tix-cil preexposure prophylaxis was offered to all LTRs based on their immunosuppressed status and increased risk of COVID-19–induced morbidity and mortality.

We compared clinical outcomes between LTRs with COVID-19 who had previously received tix-cil and those who had not. The primary outcome was the need for hospitalization, and secondary outcomes included length of hospital stay, ≥20% decline in FEV_1 3 mo after the COVID-19 diagnosis, renal failure requiring dialysis, new-onset congestive heart failure (ejection fraction <45%), venous or arterial thrombosis, intensive care unit (ICU) admission, mechanical ventilation, and COVID-19–related mortality. We propensity-score–matched patients based on baseline characteristics and therapeutic interventions; identified a matched cohort of 34 LTRs, 17 of whom were treated with tix-cil; and performed a comparative analysis of outcomes.

The study was approved by the Institutional Review Board at Norton Thoracic Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona (protocol number PHX-21-500-198-73-18 dated September 7, 2022), with waiver of patient consent. All patient care was performed under strict compliance with the ethics statement of the International Society of Heart and Lung Transplantation.

Study Participants

All adult LTRs with a first episode of COVID-19 during the study period were included (Figure 1). LTRs in the tix-cil group received preexposure prophylaxis with 2 doses of intramuscular tix-cil (150–150 mg), either at 2 separate times or simultaneously, at least 4 d before COVID-19 diagnosis. All participants were followed up until death or the end of chart abstraction in October 2022, whichever occurred earlier.

Statistical Analysis

Continuous variables are expressed as median and interquartile range (IQR) and categorical variables are expressed as count and percentage. Comparative analyses were performed using Fisher exact or chi-square tests for categorical variables and the nonparametric Kruskal–Wallis test for continuous variables. Two-tailed P values <0.05 were considered significant. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional-hazards regression model, with receipt of tix-cil as a covariate. In addition, to account for potential confounding factors that may have influenced differences in outcomes, we conducted propensity-score matching of the tix-cil and no tix-cil groups by running a logistic regression to obtain the propensity variable. We then used the nearest-neighbor method and 1:1 matching without replacement, within a caliper width of 0.2 of the standard deviation of the logit of the propensity score.[16,17] Values of standardized mean differences were used to assess pre- and postmatching imbalances, and Cohen's d values of 0.2, 0.5, and 0.8 were used to indicate measures of small, medium, and large effect sizes, respectively.[18]

We used SPSS software, version 29 for statistical analysis and the matching package from R software, version 4.2.2, for the propensity-score–matched analysis.

RESULTS

Breakthrough COVID-19

We identified 546 adult LTRs who were alive and therefore eligible for preexposure prophylaxis with tix-cil; of these, 203 received the drug between January 2022 and July 2022, and the remaining 343 either lived out of state and lacked access to tix-cil or declined tix-cil therapy. There was a trend toward reduced incidence of COVID-19 among LTRs who received tix-cil compared with eligible LTRs who did not (Figure 2). However, the difference between the 2 groups did not meet statistical significance (11.8% [24 of 203] tix-cil versus 16.6% [57 of 343] no tix-cil, HR 0.669 [95% CI, 0.415-1.079; P =

0.099]). Asymptomatic patients were not routinely screened for SARS-CoV-2 infection.

Baseline Characteristics

We identified 89 adult LTRs who developed COVID-19 during the study period: 24 received tix-cil preexposure prophylaxis and 65 did not. None of the study participants

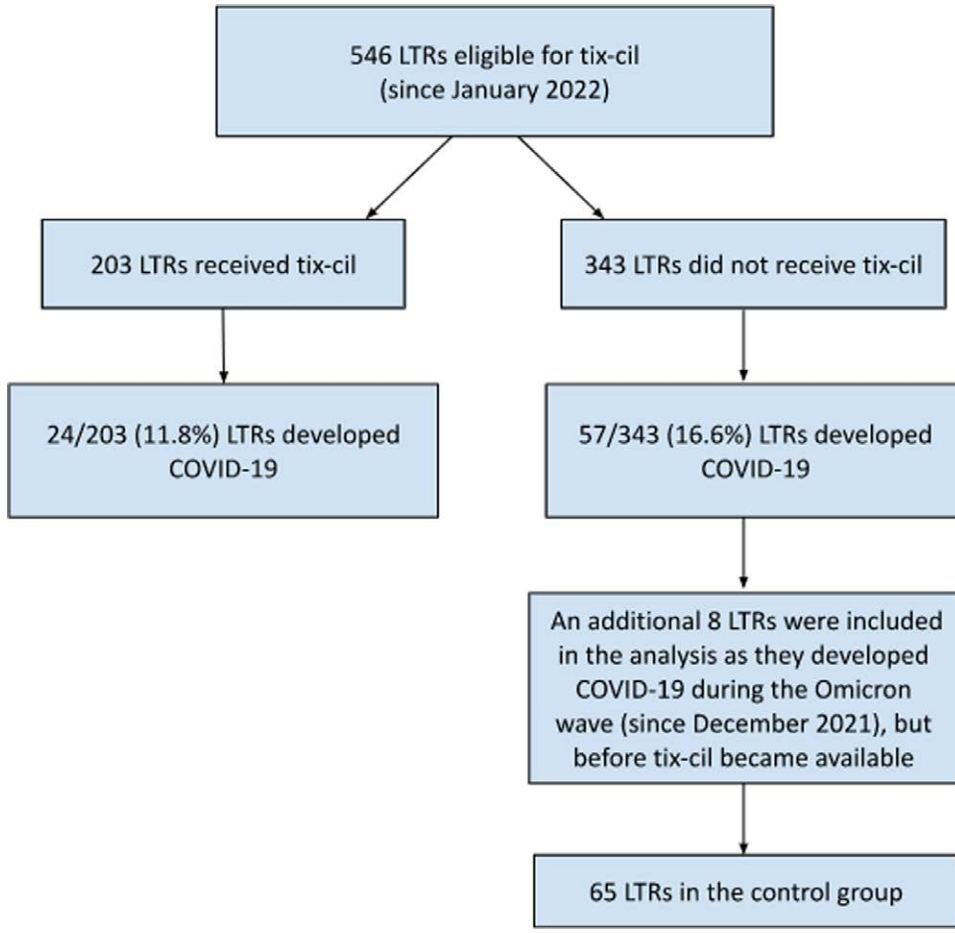

FIGURE 1. Flowchart showing selection of LTRs for the study. LTR, lung transplant recipient; tix-cil, tixagevimab-cilgavimab.

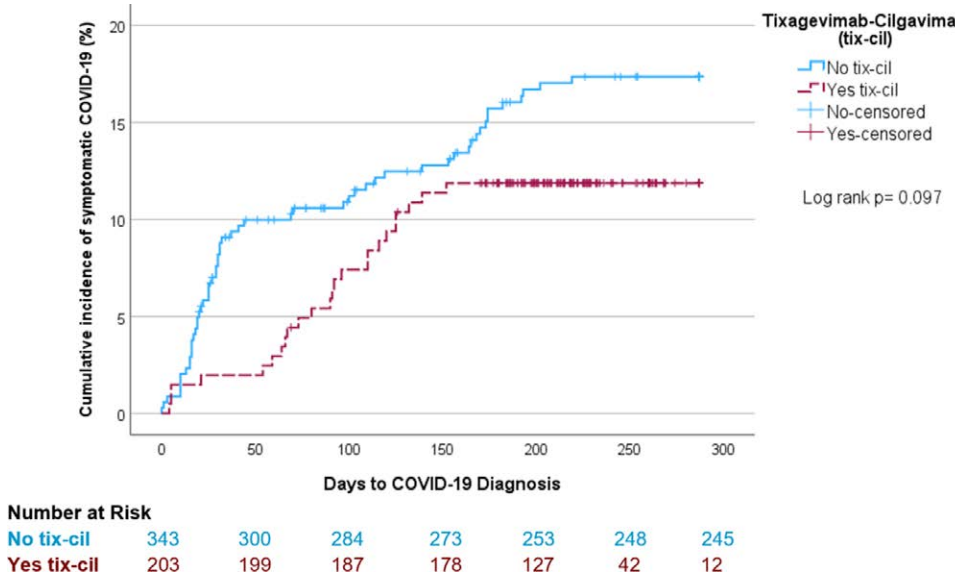

FIGURE 2. Incidence of symptomatic COVID-19 in LTRs stratified by receipt of tix-cil preexposure prophylaxis during the Omicron wave. Log rank $P = 0.097$. LTR, lung transplant recipient; tix-cil, taxagevimab-cilgavimab.

TABLE 1.

Baseline characteristics and therapeutic interventions among lung transplant recipients with COVID-19, with and without tix-cil preexposure prophylaxis

	Tix-cil, n = 24	No Tix-cil, n = 65	*P*
Baseline characteristics before COVID-19 diagnosis			
Male sex	14 (58.3)	35 (53.8)	0.812
Age at COVID-19 diagnosis, median [IQR], y	68.62 [59.02, 72.79]	67.10 [59.74, 71.97]	0.739
Blood groups			
O	8 (33.3)	23 (35.4)	0.445
A	14 (58.3)	28 (43.1)	
B	1 (4.2)	5 (7.7)	
Double lung transplant (vs single)	24 (100.0)	63 (96.9)	1.000
Time of COVID-19 diagnosis from lung transplant, median [IQR], mo	25.42 (13.85, 47.79)	38.43 (21.33, 72.63)	0.107
BMI at COVID-19 diagnosis, median [IQR], kg/m^2	26.16 [23.85, 31.78]	25.71 [22.31, 30.00]	0.509
Diabetes at COVID-19 diagnosis	15 (62.5)	33 (50.8)	0.349
CKD with eGFR <30 mL/min/1.73m^2 at COVID-19 diagnosis	2 (8.3)	10 (15.4)	0.501
Induction			
ATG	1 (4.2)	2 (3.1)	0.974
Rituximab/IVIG	4 (16.7)	12 (18.5)	
Basiliximab	17 (70.8)	44 (67.7)	
Not available	2 (8.3)	7 (10.8)	
Immunosuppressive regimen			
CNI/antiproliferative/corticosteroid	18 (75.0)	46 (70.8)	0.563
CNI/mTOR/corticosteroid	0 (0.0)	5 (7.7)	
CNI/corticosteroid	5 (20.8)	11 (16.9)	
Belatacept also included	1 (4.2)	3 (4.6)	
FEV_1 (% predicted) prior to COVID-19 diagnosis, median [IQR]	86.00 [64.75, 101.00]	88.00 [66.00, 99.00]	0.824
CLAD at COVID-19 diagnosis	5 (20.8)	10 (15.4)	0.537
BOS	4 (16.7)	9 (13.8)	0.357
RAS	1 (4.2)	0 (0.0)	
Mixed BOS and RAS	0 (0.0)	1 (1.5)	
mRNA vaccine doses before COVID-19			
<2 doses	1 (4.2)	4 (6.2)	0.237
2 doses	6 (25.0)	28 (43.1)	
>2 doses	17 (70.8)	33 (50.8)	
Therapeutic interventions at COVID-19 diagnosis			
Monoclonal antibodies	19 (79.2)	41 (63.1)	0.205
Sotrovimab	5 (20.8)	20 (30.8)	0.433
Casirivimab-imdevimab	1 (4.2)	5 (7.7)	1.000
Bamlanivimab	0 (0.0)	4 (6.2)	0.571
Bebtelovimab	14 (58.3)	12 (18.5)	**<0.001**
Antivirals	15 (62.5)	36 (55.4)	0.633
Remdesivir	2 (8.3)	22 (33.8)	**0.016**
Molnupiravir[a]	14 (58.3)	14 (21.5)	**0.002**
Increased dose of corticosteroids	23 (95.8)	59 (90.8)	0.669
Anticoagulation	24 (100.0)	62 (95.4)	0.560
Antiproliferative management at COVID-19 diagnosis			
Reduction of antiproliferative agent	4 (16.7)	6 (9.2)	0.534
Suspension of antiproliferative agent	15 (62.5)	39 (60.0)	
Not on an antiproliferative	5 (20.8)	17 (26.2)	
Tocilizumab	2 (8.3)	11 (16.9)	0.501
Tofacitinib	0 (0.0)	5 (7.7)	0.318

Data presented as no. (%), unless otherwise indicated.
Bold numbers indicate statistical significance at $P < 0.05$.
[a]One patient received both molnupiravir and remdesivir.
BMI, body mass index; BOS, bronchiolitis obliterans syndrome; CKD, chronic kidney disease; CLAD, chronic lung allograft dysfunction; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; IQR, interquartile range; mTOR, mammalian target of rapamycin inhibitor; RAS, restrictive allograft syndrome; tix-cil, tixagevimab-cilgavimab (dose: 300–300mg).

had a history of COVID-19 and none of the patients were asymptomatic. The median age was 67.4 y (59.5-72.4), 49 (55.1%) were male, 87 (97.8%) had undergone a bilateral LT, 48 (53.9%) had diabetes, 25 (28.0%) were obese (body mass index ≥30 kg/m^2), and 67 (75.3%) had chronic kidney disease (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2). The median time from LT to COVID-19 diagnosis was 36.5 mo (IQR 16.3, 70.0). The most common immunosuppressive regimen included mycophenolate mofetil, tacrolimus, and prednisone (64 [71.9%]), and the median percent

predicted FEV_1 before COVID-19 was 87% (IQR 64.5, 99.5). The overwhelming majority of patients had received at least 2 doses of an SARS-CoV-2 mRNA vaccine (84 [94.3%]).

The baseline clinical characteristics of patients with COVID-19 who received tix-cil prophylaxis and those who did not were similar (Table 1). All 24 LTRs who developed breakthrough COVID-19 had undergone bilateral LT, and 23 (95.8%) were ≥6 mo after LT; 18 (75%) were on a standard 3-drug immunosuppressive regimen with mycophenolate mofetil, tacrolimus, and prednisone. Slightly more than half of these patients (14 [58.3%]) were male, and the median age at COVID-19 diagnosis was 68.6 y. Six patients (25.0%) had received 2 doses of an mRNA vaccine and 17 (70.8%) had received ≥2 doses. The median time from tix-cil to COVID-19 diagnosis was 90.5 days (IQR, 62.75–118.25) (Figure 3).

Therapeutic Interventions

At the time of COVID-19 diagnosis, 60 (67.4%) LTRs were treated with monoclonal antibodies, 51 (57.3%) with antivirals, and 82 (92.1%) with increased corticosteroids. Typically, patients were treated with a combination of monoclonal antibodies, antivirals, augmented corticosteroids, anticoagulants, and, in cases of severe disease, immunomodulatory therapy. The choice of monoclonal antibody and antiviral agent varied depending on the dominant circulating viral sublineage, drug availability, and inpatient versus outpatient clinical setting. Patients with tix-cil prophylaxis were more likely to be treated with bebtelovimab and molnupiravir, whereas those without tix-cil prophylaxis were more likely to be treated with remdesivir (Table 1). Remdesivir was only available for hospitalized patients; LTRs who had not received tix-cil tended to have higher hospitalization rates, as described below, which explains the choice of antiviral therapy.

We performed propensity-score matching to balance the 2 groups in terms of baseline characteristics and therapeutic interventions. We obtained 17 LTRs in the tix-cil group and matched them with 17 LTRs in the non–tix-cil group based on age, sex, body mass index, diabetes, eGFR <30 mL/min/1.73 m^2, sotrovimab, bebtelovimab, and molnupiravir therapies with a small effect size and number of SARS-CoV-2 mRNA vaccine doses and remdesivir therapy with a medium effect size (Table 2).

Clinical Outcomes in the Unmatched Groups

Of the 24 LTRs with COVID-19 who had received tix-cil prophylaxis, 5 (20.8%) were hospitalized, 3 (12.5%) required ICU level of care, 2 (8.3%) were intubated, and 2 (8.3%) died. Both patients who died were male and >70 y old, had received 2 doses of an mRNA vaccine, and were >2 y out from LT. Both had preexisting diabetes mellitus and chronic renal insufficiency (eGFR of 47 and 24 mL/min/1.73 m^2); both were treated with corticosteroids and tocilizumab; and 1 received antiviral and monoclonal antibody therapy with remdesivir and sotrovimab, respectively. Both required ICU level of care and 1 was intubated. These 2 LTRs received a COVID-19 diagnosis 64 and 139 d after tix-cil and died 91 and 12 d later, respectively.

There was a trend toward a lower rate of hospitalization among the 24 LTRs who had received tix-cil compared with the 65 LTRs who had not received tix-cil prophylaxis; however, the results did not reach statistical significance (20.8% versus 43.1%, HR, 0.430; 95% CI, 0.165-1.118; $P = 0.083$). The length of hospital stay, ≥20% decline in FEV_1 3 mo after COVID-19 diagnosis, incidence of renal failure requiring dialysis, new-onset congestive heart failure (ejection fraction < 45%), and venous or arterial thrombosis did not differ

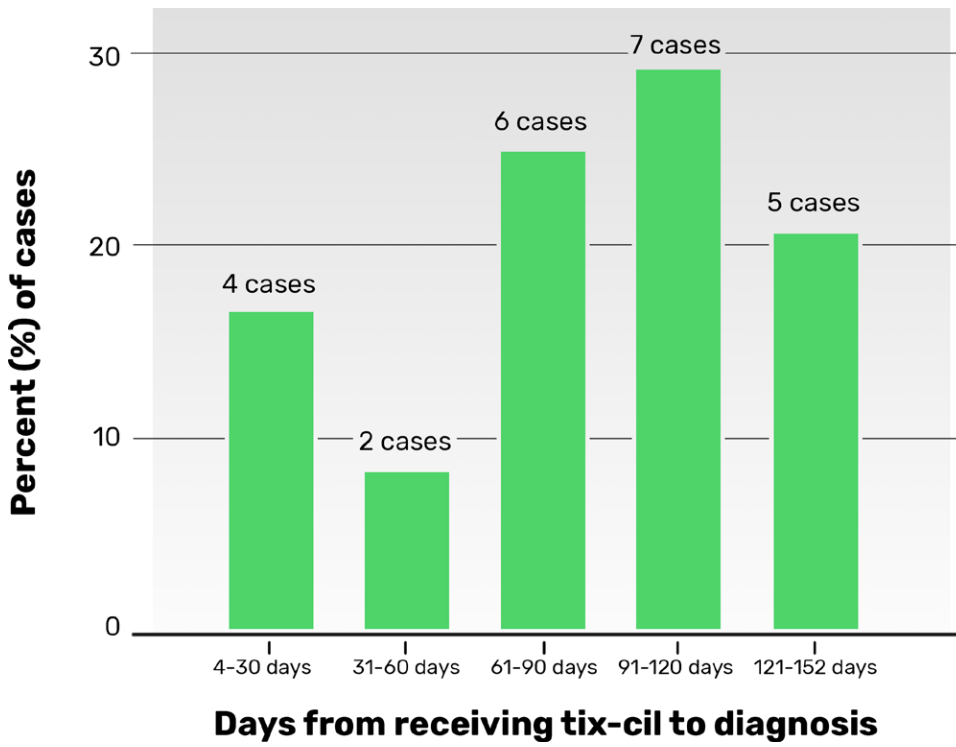

FIGURE 3. Bar graph showing time between receipt of tixagevimab-cilgavimab prophylaxis and diagnosis of COVID-19 among lung transplant recipients. Tix-cil, tixagevimab-cilgavimad.

significantly between the groups. The 2 groups also had similar rates of ICU admission (HR, 0.878; 95% CI, 0.238-3.244; $P = 0.845$) and intubation with mechanical ventilation (HR, 1.320; 95% CI, 0.242-7.210; $P = 0.749$) (Table 3). Notably, COVID-19–related mortality was high in both groups (2 in the tix-cil group [8.3%] and 10 in the no tix-cil group [15.4%]; Table 3) and the difference was not statistically significant (HR, 0.601; 95% CI, 0.130-2.773; $P = 0.514$).

Clinical Outcomes in Propensity-score–matched Groups

We included 34 patients in the propensity-score–matched analysis with 17 matched LTRs in the tix-cil group and 17 in the no tix-cil group (Table 2). In the propensity-matched analysis, both groups had high rates of hospitalization (HR, 0.468; 95% CI, 0.156-1.402; p= 0.175; Figure 4), ICU admission (HR, 3.096; 95% CI, 0.322-29.771; $P = 0.328$), intubation with mechanical ventilation (HR, 1.958; 95% CI, 0.177-21.596; $P = 0.583$), and death (HR, 1.015; 95% CI, 0.143-7.209; $P = 0.988$). The 2 propensity-score matched groups had similar COVID-19–related mortality rates: 2 in the tix-cil group (11.8%) and 2 in the non–tix-cil group (11.8%) died (Table 3; Figure 5).

DISCUSSION

COVID-19 carries a high risk of morbidity and mortality among LTRs due to their advanced immunosuppression, reduced response to vaccination, and compromised pulmonary mucociliary clearance.[1,19-22] This study identified a significant number of breakthrough SARS-CoV-2 infections among LTRs who received tix-cil preexposure prophylaxis (24 of 203 [11.8%]). Furthermore, tix-cil preexposure prophylaxis did not reduce COVID-19 severity among LTRs who

TABLE 2.

Covariates included in propensity-score matching

Covariates	Tix-cil (n = 17)	No tix-cil (n = 17)	*P*	Standardized mean difference[a]
Baseline characteristics before COVID-19 diagnosis				
Age, mean [IQR], y	67.50 [59.56, 73.86]	67.43 [59.44, 70.53]	0.904	0.037
Sex, male	11 (64.7)	10 (58.8)	1.000	0.121
BMI, mean [IQR], kg/m^2	26.70 [21.56, 31.74]	27.34 [22.60, 31.59]	0.730	0.144
Diabetes	13 (76.5)	11 (64.7)	0.708	0.260
CKD with eGFR <30 mL/min/1.73 m^2	2 (11.8)	3 (17.6)	1.000	0.167
mRNA vaccine doses				
<2 doses	1 (5.9)	0 (0)	0.259	0.583
2 doses	6 (35.3)	3 (17.6)		
>2 doses	10 (58.8)	14 (82.4)		
Therapeutic interventions at COVID-19 diagnosis				
Monoclonal antibody therapy	12 (70.6)	13 (76.5)	1.000	0.134
Sotrovimab	5 (29.4)	4 (23.5)	1.000	0.134
Bebtelovimab	7 (41.2)	6 (35.3)	1.000	0.121
Molnupiravir	7 (41.2)	8 (47.1)	1.000	0.119
Remdesivir	2 (11.8)	4 (23.5)	0.656	0.312

Data presented as no. (%), unless otherwise indicated.
[a]Effect sizes interpreted based on Cohen's d values as small (Cohen's d = 0.2), medium (Cohen's d = 0.5), and large (Cohen's d = 0.8).[15]
BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; tix-cil, tixagevimab-cilgavimab (dose: 300–300 mg).

TABLE 3.

Clinical outcomes of lung transplant recipients with COVID-19, with and without tix-cil preexposure prophylaxis

Outcomes	Unmatched study groups			Propensity-score–matched study groups		
	Tix-cil (n = 24)	No tix-cil (n = 65)	*P*	Tix-cil (n = 17)	No tix-cil (n = 17)	*P*
Hospitalization	5 (20.8)	28 (43.1)	0.082	5 (29.4)	9 (52.9)	0.296
Duration of hospitalization, median [IQR], d	7.00 [4.00, 12.00]	11.00 [6.50, 17.00]	0.247	7.00 [4.00, 12.00]	7.00 [2.00, 8.00]	0.737
≥20% decline in FEV_1 ≥3 mo after COVID-19[a]	0 (0)	6 (9.2)	0.185	0 (0)	1 (5.9)	1.000
Renal failure with need for RRT	1 (4.2)	7 (10.8)	0.440	1 (5.9)	2 (11.8)	1.000
New-onset CHF with EF <45%	0 (0)	1 (1.5)	1.000	0 (0)	1 (5.9)	1.000
Venous or arterial thrombosis	0 (0)	6 (9.2)	0.185	0 (0)	2 (11.8)	0.485
ICU admission	3 (12.5)	9 (13.8)	1.000	3 (17.6)	1 (5.9)	0.601
Intubation and mechanical ventilation	2 (8.3)	4 (6.2)	0.659	2 (11.8)	1 (5.9)	1.000
COVID-19–related death	2 (8.3)	10 (15.4)	0.501	2 (11.8)	2 (11.8)	1.000

Data presented as no. (%), unless otherwise indicated.
[a]FEV1 ≥3 mo after COVID-19 was not available for 10 patients who died before spirometry was performed, or for 5 patients without available follow-up spirometry data at the conclusion of chart abstraction in October 2022.
CHF, congestive heart failure; EF, ejection fraction; FEV_1, forced expiratory volume in 1 s; ICU, intensive care unit; IQR, interquartile range; RRT, renal replacement therapy; tix-cil, tixagevimab-cilgavimab (dose: 300–300 mg).

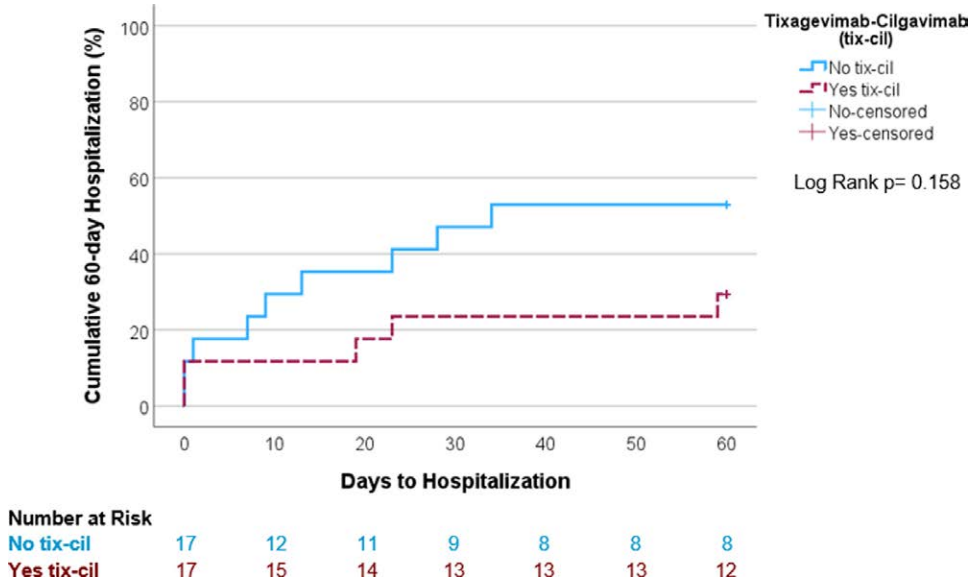

FIGURE 4. Kaplan Meier curve for COVID-19–related hospitalization of propensity-matched lung transplant recipients with and without tixagevimab-cilgavimab (tix-cil) preexposure prophylaxis.

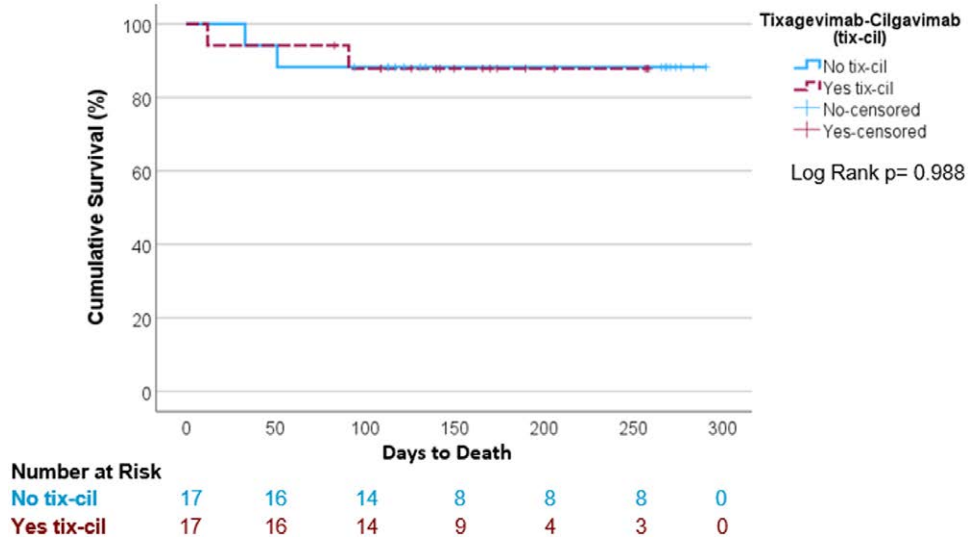

FIGURE 5. Kaplan Meier curve for post-COVID-19 survival of propensity-matched lung transplant recipients with and without tixagevimab-cilgavimab (tix-cil) preexposure prophylaxis (both groups had 88.2% survival at 1 y after COVID-19. Log rank $P = 0.988$).

developed a breakthrough infection (Table 3). These findings are in contrast with the results of several large clinical trials (Table 4) and highlight the need for more effective prophylactic strategies to combat COVID-19 in vulnerable patients.

The PROVENT trial included 5197 participants in a 2:1 randomization of tix-cil to placebo. Compared with placebo, tix-cil preexposure prophylaxis reduced the risk of developing symptomatic COVID-19 by 77% (95% CI, 46-90).[15] However, despite the trial's large sample size, only 172 (3.3%) of the participants were on immunosuppressive therapy, and only 3 of these developed COVID-19 during the study period, thereby limiting generalizability to solid organ transplant recipients. In addition, the Alpha and Delta variants were predominant during the PROVENT trial, which was conducted between November 2020 and August 2021, whereas Omicron prevailed when the FDA authorized tix-cil.

The Omicron variant (B.1.1.529) carries numerous mutations in its spike protein and has evolved into more than 100 sublineages, including BA.1.1, BA.2, and BA.5.[28] The BA.1.1 sublineage was predominant in early 2022; however, by April 2022, almost all infections were caused by BA.2 and starting in July 2022 by BA.5.[2] A French team evaluated tix-cil–based neutralization and reported that tix-cil neutralizing activity of Omicron sublineages was reduced.[29] Furthermore, compared with the anti-Delta activity, the anti-Omicron activity was markedly lower against BA.1.1 (176-fold) than BA.2 (5.4-fold) or BA.5 (2.8- to 16-fold).[9,13,14] Patients in our study were diagnosed with COVID-19 between December 2021 and August 2022, a period during which BA.1.1, BA.2, BA.2.12.1, and BA.5 sublineages were predominant, which likely explains our higher rates of breakthrough COVID-19 compared with the PROVENT trial.

TABLE 4.

Summary of pertinent literature

Reference	Country	Study design and objective	Study period prevalent SARS-CoV-2 strain	Study population	Endpoints	Results	Remarks
Levin et al[15] (PROVENT trial)	USA	Phase III randomized, double-blind, placebo-controlled, multicenter study Assessed safety and efficacy of tix-cil PrEP compared with placebo for prevention of COVID-19	November 2020–March 2021 Alpha and Delta	Total: 5197 Tix-cil: 3460 Placebo: 1737 Unvaccinated adults Immunosuppressed: Total: 172 (3.3%) Tix-cil: 109 (3.2%) Placebo: 63 (3.6%)	Primary safety endpoint: Adverse events Primary efficacy endpoint: First episode of COVID-19	Primary safety endpoint: No serious safety concerns Primary efficacy endpoint: COVID-19: Tix-cil: 8 of 3441 (0.2%) Placebo: 17 of 1731 (1.0%) RRR: 76.7%; (95% CI, 46.0-90.0); $P < 0.001$ 82.8% (95% CI, 65.8-91.4) on extended follow-up at a median of 6 mo Subgroup analysis did not show efficacy among immunosuppressed patients, RRR: 71.7% (95% CI, −301.0 to 98.0)	Tix-cil dose: 150–150 mg Tix-cil PrEP reduced the risk of COVID-19 as compared with placebo. Results of the trial may not be generalizable to Omicron variant or to LTRs given low event rates in the immunosuppressed subgroup
Najjar-Debbiny et al[23]	Israel	Retrospective cohort study Examined efficacy of tix-cil PrEP in preventing SARS-CoV-2 infection and hospitalization for COVID-19 in immunocompromised patients	February 2022–June 2022 Omicron	Total: 3515 Tix-cil: 703 Placebo: 2812 Adult SOTRs Tix-cil: 245 (34.9%) No tix-cil: 966 (34.4%) Chronic lung disease: Tix-cil: 93 (13.2%) No tix-cil: 337 (12%)	Endpoints: SARS-CoV-2 infection Hospitalization for COVID-19	SARS-CoV-2 infection: tix-cil 72 of 703 (10.2%) No tix-cil 377 of 2812 (13.4%) HR 0.75 (95% CI, 0.58-0.96); $P = 0.023$ Hospitalization: Tix-cil: 7 of 72 (9.7%) No tix-cil: 67 of 377 (17.8%) HR 0.41 (95% CI, 0.19-0.89); $P = 0.025$	Tix-cil dose: 150–150 mg Tix-cil did not reduce COVID-19 risk in patients with chronic lung disease (HR 1.12 [95% CI, 0.86-20.4]) Efficacy of tix-cil was not reported for SOTRs
Kertes et al[24]	Israel	Retrospective observational study Examined efficacy of tix-cil PrEP in preventing SARS-CoV-2 infection and severe COVID-19 in immunocompromised patients	December 2021–April 2022 Omicron	Total: 5124 Tix-cil: 825 Controls: 4299 ≥12 y old immunosuppressed individuals SOTRs Tix-cil: 334 (40.5%) No tix-cil: 1354 (31.5%)	Endpoints: SARS-CoV-2 infection Hospitalization for COVID-19 All-cause mortality	SARS-CoV-2 infection: Tix-cil: 29 of 825 (3.5%) No tix-cil: 308 of 4299 (7.2%) (OR 0.51; 95% CI, 0.30-0.84) Hospitalization for COVID-19: Tix-cil: 1 of 825 (0.1%) No tix-cil: 27 of 4299 (0.6%) All-cause mortality: Tix-cil: 0 of 825 No tix-cil: 40 of 4299 (0.9%) Hospitalization/death (OR 0.08; 95% CI, 0.01-0.54)	Tix-cil dose: 150–150 mg Types of SOTRs were not specified. Patients who had received tix-cil PrEP were 49% less likely to become infected with SARS-CoV-2 and 92% less likely to be hospitalized or die
Nguyen et al[25]	France	Observational multicenter cohort study Described incidence of COVID-19 and its outcomes among immunocompromised patients receiving tix-cil PrEP	December 2021–March 2022 Omicron	Total: 1112 (all received tix-cil) SOTRs 631 (56.7%) KTRs 511 (46%) HTRs 83 (7.5%) LTRs 36 (3.2%) LiTRs 1 (0.1%)	Endpoints: SARS-CoV-2 infection Disease severity All-cause mortality	SARS-CoV-2 infection: 49 of 1112 (4.4%) Mild to moderate illness: 43 of 49 (88%) Moderate-to-severe illness: 6 of 49 (12%) Death: 2 of 49 (4%)	Tix-cil dose: 150–150 mg Short follow-up, median 63 (49–73) d Immunocompromised study population, but only a small number of LTRs No control group for comparative analysis

Ordaya et al[26]	USA	Descriptive analysis Described the incidence of COVID-19 and its outcomes among immunocompromised patients receiving tix-cil PrEP	January 2022–February 2022 Omicron	Total: 674 (all received tix-cil) Immunosuppressed adults SOTRs: 148 (22%)	Endpoints: SARS-CoV-2 infection Hospitalization for COVID-19 All-cause mortality	SARS-CoV-2 infection: 8 of 674 (1.2%) Hospitalization for COVID-19: 2 of 8 (25%) Death: 0	Tix-cil dose: 150–150 mg Immunocompromised study population, but only 1 heart and lung transplant recipient developed COVID-19 No control group for comparative analysis
Benotmane et al[27]	France	Case series Described clinical experience with tix-cil PrEP in KTRs	December 2021–March 2022 Omicron	Total: 416 KTRs (all received tix-cil)	Endpoints: SARS-CoV-2 infection Hospitalization for COVID-19 COVID-19–related mortality	SARS-CoV-2 infection: 39 of 419 (9.4%) Hospitalization:14 of 39 (35.9%) ICU admission: 3 of 39 (7.7%) Death: 2 of 39 (5.1%) Limited neutralizing activity against Omicron variant, recommendation for increased dose of tix-cil.	Tix-cil dose: 150–150 mg No control group for comparative analysis
Current study	USA	Retrospective cohort study Examined whether tix-cil PrEP reduced the incidence or disease severity of COVID-19 in LTRs	December 2021–August 2022 Omicron	Total: 546 adult LTRs Tix-cil: 203 LTRs (37.2%) No tix-cil: 343 LTRs (62.8%)	End points: First episode of COVID-19 Hospitalization, ICU admission, and intubation for COVID-19 COVID-19-related mortality	First episode of COVID-19 Tix-cil: 24 of 203 (11.8%) No tix-cil: 57 of 343 (16.6%) HR 0.669 (95% CI, 0.415-1.079), $P = 0.099$ Unmatched groups: Hospitalization: Tix-cil: 5 of 24 (20.8%) No tix-cil: 28 of 65 (43.1%) (HR 0.430; 95% CI, 0.165-1.118; $P = 0.083$) ICU admission: 3 of 24 (12.5%) vs 9 of 65 (13.8%) (HR 0.878; 95% CI, 0.238-3.244; $P = 0.845$) Intubation: 2 of 24 (8.3%) vs 4 of 65 (6,2%) (HR, 1.320; 95% CI, 0.242-7.210; $P = 0.749$) Death: 2 of 24 (8.3%) vs 10 of 65 (15.4%) (HR, 0.601; 95% CI, 0.130-2.773; $P = 0.514$). Propensity-matched analysis: Hospitalization: HR, 0.468; 95% CI, 0.156-1.402; $P = 0.175$ ICU admission: HR, 3.096; 95% CI, 0.322-29.771; $P = 0.328$ Intubation: HR, 1.958; 95% CI, 0.177-21.596; $P = 0.583$ Death: HR, 1.015; 95% CI, 0.143-7.209; $P = 0.988$	Tix-cil dose: 300–300 mg (higher dose than previous studies) There was a trend toward a lower incidence of COVID-19 and COVID-19 related hospitalization among unmatched LTRs that received tix-cil during the Omicron wave. In the propensity-matched analysis, tix-cil did not reduce disease severity in LTRs with breakthrough COVID-19 and COVID-19–related mortality was high (11.8%) during the Omicron wave. This is the first study to focus on LTRs, a vulnerable patient population with advanced immunosuppression and compromised respiratory mechanics

CI, confidence interval; HR, hazard ratio; HTR, heart transplant recipient; KTR, kidney transplant recipient; LiTR, liver transplant recipient; LTR, lung transplant recipient; OR, odds ratio; PrEP, preexposure prophylaxis; RRR, relative risk reduction; SOTR, solid organ transplant recipient; tix-cil, tixagevimab-cilgavimab.

Using data maintained by the Clalit Health Services and the Israeli Ministry of Health, Najjar-Debbiny and colleagues[23] propensity-score–matched 703 immunosuppressed adults who received tix-cil with a control group of 2812 patients who did not. Follow-up started at the date of tix-cil treatment in mid-February 2022, while Omicron was the main circulating variant, and continued for up to 90 d or June 30, 2022, whichever came first. Overall, 72 patients in the tix-cil group (10.2%) and 377 patients in the control group (13.4%) were infected by SARS-CoV-2, reflecting an HR of 0.75 (95% CI, 0.58-0.96) for SARS-CoV-2 infection and 0.41 (95% CI, 0.19-0.89) for COVID-19–related hospitalization in the tix-cil group compared with the control group. Another Israeli study by Kertes et al[24] reported that 825 immunocompromised adults who received tix-cil had a lower rate of SARS-CoV-2 infection than 4299 immunocompromised adults who did not receive tix-cil (29 [3.5%] versus 308 [7.2%], $P < 0.001$). Furthermore, moderate-to-severe COVID-19 was uncommon in the tix-cil group, with 1 (0.1%) person hospitalized for COVID-19 compared with 27 (0.6%) in the non–tix-cil group ($P = 0.07$). No mortality was recorded in the tix-cil group, whereas 40 deaths (0.9%) occurred in the non–tix-cil group ($P = 0.005$). The incidence of breakthrough SARS-CoV-2 infection in our study mirrored that of the Najjar-Debbiny et al study,[23] likely reflecting the reduced efficacy of tix-cil at preventing Omicron-driven COVID-19 in immunocompromised patients. Notably, unlike Najjar-Debbiny et al and Kertes et al,[23,24] we did not identify a reduced risk of hospitalization among tix-cil recipients compared with those who did not receive PrEP. In addition, our propensity-score matched analysis showed that PrEP with tix-cil did not reduce hospitalization rates, ICU admissions, the need for mechanical ventilation, or death among LTRs with COVID-19. Importantly, Najjar-Debbiny et al[23] did not find a protective effect of tix-cil preexposure prophylaxis among patients with chronic lung disease, which supports the findings of our study and highlights the unique vulnerability of LTRs to COVID-19–associated morbidity and mortality.

Patients vaccinated against SARS-CoV-2 were excluded from the PROVENT trial,[15] but not from the study led by Najjar-Debbiny et al[23]; in fact, 74.3% of patients who received tix-cil were adequately vaccinated before tix-cil treatment. This high vaccination rate mirrors that of our patient population with 23 of 24 patients (95%) with breakthrough COVID-19 having had at least 2 mRNA vaccines before tix-cil prophylaxis. This is likely explained by the increased ability of the Omicron variant to evade both vaccine-induced immunity and tix-cil compared with that of the Alpha or Delta variants. However, it is also possible that exposure rates were significantly higher during the months in which the Omicron variant was predominant.

To date, large studies illustrating the impact of tix-cil PrEP on COVID-19 severity among solid organ transplant recipients are largely lacking. A French study of 1112 immunocompromised patients reported 49 breakthrough infections (4.4%), including 24 in solid organ transplant recipients, 3 of whom were LTRs[25]; 4 of the 24 solid organ transplant recipients (16.7%) developed moderate-to-severe COVID-19, and all 4 were kidney transplant recipients. The 3 LTRs had a mild illness. A study from the Mayo Clinic included 674 immunocompromised patients who received tix-cil prophylaxis, including 148 solid organ transplant recipients, 3 of whom developed a breakthrough SARS-CoV-2 infection.[26] One patient had mild COVID-19 and 2 were asymptomatic. These results contrast with our findings: 5 (20.8%) of our patients required hospitalization, 3 (12.5%) required ICU level of care, 2 (8.3%) required mechanical ventilation, and 2 (8.3%) died. Last, Benotmane et al[27] reported on 416 kidney transplant recipients who received low-dose tix-cil prophylaxis (150mg-150mg). They identified 39 (9.4%) patients with breakthrough COVID-19, with 14 (35.9%) requiring hospitalization, 3 (7.7%) ICU admissions, and 2 (2.1%) deaths. Importantly, we noted similar disease severity despite our cohort receiving the reportedly more effective high-dose (300–300mg) tix-cil prophylaxis.

Our study has some limitations. First, our study is relatively small and likely underpowered to detect small effect sizes. However, because LTRs represent a very small segment of the population, it is difficult to obtain an adequate sample size, particularly in a single-center retrospective analysis. In addition, although our study may be underpowered, its findings remain important as they emphasize the need for ongoing COVID-19 precautions despite tix-cil preexposure prophylaxis as breakthrough infections and severe disease remained common despite tix-cil. Second, patients were not screened for asymptomatic SARS-CoV-2 infection, which could have influenced our results. Third, the efficacy of therapeutic interventions is best assessed in randomized controlled trials. Finally, behavioral practices, including reduced rates of masking and social distancing, during the latter periods of the pandemic cannot be accounted for in this study and may have contributed to higher COVID-19 infection rates.

In conclusion, our study found that despite high-dose tix-cil preexposure prophylaxis, the rate of breakthrough SARS-CoV-2 infection was high, and moderate to severe breakthrough COVID-19 was common among LTRs. Furthermore, the severity of COVID-19 in LTRs who received tix-cil prophylaxis and those who did not was similar. The efficacy of monoclonal antibody therapy at preventing SARS-CoV-2 infection and reducing COVID-19 severity is likely limited by mutations in the viral spike protein and the patient's degree of immunosuppression. Furthermore, LTRs are a unique patient population as they are at a particularly high risk of respiratory infections not only due to their high degree of immunocompromise, but also due to impaired respiratory mechanics including ciliary dysfunction, tracheobronchomalacia, airway stenoses, and impaired cough. Last, in vitro viral neutralization studies do not factor in the patients' degree of immune compromise and, therefore, may not mirror real-world therapeutic efficacy. Therapies targeting more stable and less mutation-prone viral epitopes are needed as are more effective antiviral therapies with fewer drug–drug interactions.

ACKNOWLEDGMENTS

The authors thank Kristine Nally for editorial assistance and Marco Marchionni for graphic design.

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