Original Article

COVID-19 caused by the Omicron variant in lung transplant recipients: a single center case series

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Background: Although coronavirus disease 2019 (COVID-19) is no longer classified as a Public Health Emergency of International Concern by World Health Organization, its global impact persists. Data on its impact in lung transplant recipients (LTRs) from China remain limited. This study aims to share clinical experiences and provide insights into managing LTRs with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Methods: We conducted a study on LTRs with COVID-19 caused by the Omicron variant from November 17, 2022, to May 1, 2023. Clinical information was gathered retrospectively through electronic medical records, questionnaires, or follow-up telephone calls.

Results: A total of 227 LTRs were reviewed for infection with Omicron variant. After excluding 49 cases without confirmed SARS-CoV-2 infection, this left a final cohort of 178 infected LTRs, accounting for an infection rate of 78.4% (178/227). Of the patients, 50% (89/178) required hospitalization, with an average hospital stay of 16 days [interquartile range (IQR): 9.5–25.5 days]. Of the 89 hospitalized patients, 41.6% (37/89) eventually progressed to severe or critical disease, forming the severe/critical group (S/C group), while the remaining 58.4% (52/89) had mild or moderate disease (M/M group). In comparison to the M/M group, the S/C group had higher C-reactive protein (CRP) (59.6 *vs.* 16.8 mg/L, P<0.001), Erythrocyte sedimentation rate (45.5 *vs.* 22.5 mm/h, P=0.005) and D-dimer level (1.09 *vs.* 0.65 mg/L, P=0.01), but lower $CD4^+$ T lymphocytes count (217 *vs.* 427 cells/μL, P=0.004). The S/C group had significantly higher rates of combined pulmonary bacterial infection (67.6% *vs.* 38.5%, P=0.006) and pulmonary fungal infection (73.0% *vs.* 38.5%, P=0.001) during the course of COVID-19, nearly double that of the M/M group. In a multivariate logistic analysis, elevated CRP (>41.8 mg/L), combined pulmonary fungal infection, and interstitial lung disease (ILD) as primary disease emerged as high-risk factors for developing the severe disease phenotype following Omicron variant infection in LTRs, with respective odds ORs values of 4.23 [95% confidence interval (CI): 1.68–11.23], 4.76 (95% CI: 1.59–15.64), and 5.13 (95% CI: 1.19–29.17). Receiver operating characteristic (ROC) curve analysis showed that $CD4^+$ T lymphocyte count may be a strong marker for predicting death. At a cutoff of 404 cells/μL, sensitivity was 0.509, specificity 0.999, and area under the curve (AUC) was 0.806 (95% CI: 0.678–0.934). Ultimately, 13 recipients succumbed to COVID-19 related respiratory failure or secondary multiple organ dysfunction, resulting in an overall mortality rate of 7.3% (13/178).

Conclusions: LTRs are at high risk of secondary lung infections after Omicron. Key risk factors for

severe disease include CRP >41.8 mg/L, ILD as primary disease, and pulmonary fungal infection. CD4+ T lymphocyte count may predict mortality risk in LTRs with COVID-19.

Keywords: Lung transplantation; Omicron; coronavirus disease 2019 (COVID-19); coronavirus; risk factor

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Introduction

Although coronavirus disease 2019 (COVID-19) is no longer classified as a Public Health Emergency of International Concern by World Health Organization (WHO), its global impact persists. The causative virus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), continues to evolve, generating new variants that contribute to ongoing morbidity and mortality (1). Among the most vulnerable to these ongoing challenges are solid organ transplant (SOT) recipients, who depend on long-term immunosuppressive medications to prevent graft rejection. It is noteworthy that lung transplant recipients (LTRs) have the highest risk of community-acquired respiratory viral infections (2). These patients are uniquely susceptible to severe disease due to their altered immune responses, making them a critical population for studying the impacts of emerging SARS-CoV-2 variants.

In November 2021, the emergence of the Omicron variant of SARS-CoV-2 marked a turning point in the pandemic. Rapidly classified as a Variant of Concern (VOC) by WHO, Omicron introduced a high number of mutations in its spike protein, leading to increased transmissibility and the ability to evade immunity from prior infections and vaccinations (3-5). By December 2021, the first cases of Omicron infection were identified in mainland China, and the variant quickly dominated the local epidemiological landscape, becoming the predominant strain in the following year (6). While Omicron's pulmonary pathogenicity and lethality were substantially reduced compared to earlier VOCs such as Delta, its widespread circulation presented new challenges for managing vulnerable populations (3,4,7).

Comorbidities play a crucial role in determining the prognosis of individuals affected by COVID-19 (8-10). Immunosuppressive states, particularly in SOT recipients, require special attention due to the complex interaction between the virus and the immune system (11-19). While limited researches on LTRs following SARS-CoV-2 infection have shown heterogeneity in clinical presentations, disease severity, and outcomes (20-27), data on COVID-19 in LTRs from China, especially during the Omicron-dominant period, remain scarce. This study aims to share clinical experiences and provide insights into managing LTRs during the Omicron wave, which may help inform future clinical strategies for this specific patient population.

Highlight box

Key findings

- C-reactive protein (CRP) >41.8 mg/L, interstitial lung disease (ILD) as primary disease, and combined pulmonary fungal infection are high-risk factors for developing severe disease in lung transplant recipients (LTRs) with coronavirus disease 2019 (COVID-19) caused by the Omicron variant. $CD4^+$ T lymphocyte count <404 cells/μL may predict mortality risk.

What is known and what is new?

- We have known that solid organ transplant recipients who contracted severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) are susceptible to severe disease mainly due to immunosuppressive treatment. Although recent reports have highlighted reduced morbidity and mortality associated with the Omicron variant, its impact on LTRs remains substantial. However, a limited number of studies on LTRs have been reported, especially from Chinese experience.
- In this study, we showed that LTRs displayed an increased vulnerability to combined lung bacterial or fungal infections following Omicron infection. CRP >41.8 mg/L, ILD as primary disease, and combined pulmonary fungal infection are recognized as high-risk factors for developing severe disease after Omicron infection. $CD4^+$ T lymphocyte count <404 cells/μL may predict mortality risk.

What is the implication, and what should change now?

- Although COVID-19 is no longer classified as a Public Health Emergency of International Concern by World Health Organization, it is still mutating and causing death, especially in immunocompromised people.
- We emphasize the importance for dynamic surveillance and timely intervention measures in the care of LTRs affected by SARS-CoV-2, in light of the challenges posed by the Omicron variant or other variants in the future.

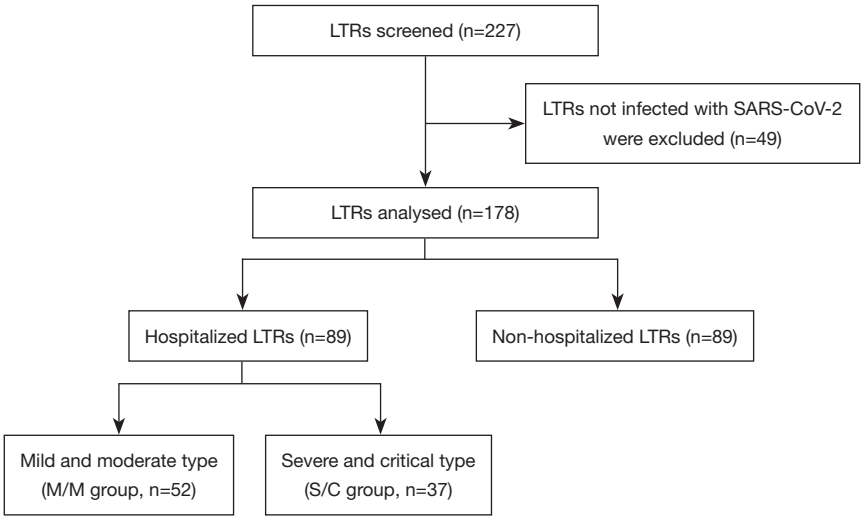

Figure 1 Flow diagram of cases inclusion and exclusion. LTRs, lung transplant recipients; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1314/rc).

Methods

Subjects

A total of 227 LTRs were reviewed for infection with Omicron variant, and none of them had been infected with SARS-CoV-2 before November 17, 2022. The inclusion criteria required symptom onset after November 17, 2022, when the Omicron variant became dominant in China, accounting for over 99% of nationwide infections (6). The LTRs were instructed to promptly notify their attending physicians if they suspected or confirmed a COVID-19 diagnosis, whether through self-testing or public health facilities. After excluding 49 cases without confirmed SARS-CoV-2 infection, we conducted a single-center, retrospective study of 178 adult LTRs with confirmed SARS-CoV-2 infection from November 17, 2022, the date of the first diagnosis, until the end of the study period on May 1, 2023.

The decision for hospitalization was guided by disease severity and available medical resources, adhering to the principle of "hospitalization and treatment for those in need". All patients with severe or critical conditions, and some with mild or moderate symptoms, were admitted to the hospital. Among the confirmed cases, 89 were hospitalized, while the remaining 89 were managed in outpatient or community settings (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of China-Japan Friendship Hospital (No. 2022-KY-148) and informed consent was taken from all the patients.

Data collection

Data on 89 non-hospitalized LTRs with SARS-CoV-2 infection were primarily collected through online questionnaires or telephone follow-up, focusing on demographic characteristics and clinical symptoms. In contrast, clinical data for 89 hospitalized LTRs with SARS-CoV-2 infection were obtained by reviewing electronic medical records. The collected data encompassed the following key aspects:

(I) Demographic characteristics: COVID-19 vaccination status and details of the immunosuppressive regimen were included.
(II) Clinical symptoms: symptoms were considered COVID-19-related if they began at the time of COVID-19 onset, were absent prior to infection, or worsened after infection.
(III) Laboratory examinations: for inpatients, a comprehensive set of laboratory results within 48 hours of admission was gathered, covering blood routine analyses, myocardial enzyme indicators, inflammatory markers, immunoglobulin levels, and more.

(IV) Respiratory support methods: detailed information on the type of respiratory support provided to each patient was recorded.
(V) Treatments: the specific antiviral and anti-inflammatory treatments administered to each patient were documented.
(VI) COVID-19-associated complications and prognosis: secondary pulmonary infections were defined as new infections identified 48 hours after admission. Co-infections referred to infections diagnosed at the time of admission. It is noteworthy that this study did not differentiate between these two types of infections but rather provided an overarching perspective on the co-occurrence of COVID-19 and other infections during hospitalization.

Diagnosis of COVID-19

Referring to the "Diagnosis and Treatment Program for Novel Coronavirus Infection (Trial Version 10)" as issued by National Health Commission of the People's Republic of China (28), the diagnosis of SARS-CoV-2 infection was established through a comprehensive assessment that integrated epidemiological history, clinical manifestations, and laboratory findings. Confirmation of SARS-CoV-2 infection in LTRs was based on the following criteria: (I) clinical manifestations: clinical signs and symptoms consistent with novel coronavirus infection; (II) laboratory testing: positive results for novel coronavirus nucleic acid testing or novel coronavirus antigen testing. For non-hospitalized patients, SARS-CoV-2 infection was diagnosed through self-administered antigen testing.

Based on the "Diagnosis and Treatment Program for Novel Coronavirus Infection (Trial Version 10)" (28), the clinical classification of COVID-19 typically comprises four categories: mild, moderate, severe, and critical. Due to the limited number of patients in each category, we combined the mild and moderate cases into a single group, referred to as the "mild/moderate" (M/M) group. Patients in this group had a respiratory rate of fewer than 30 breaths per minute and oxygen saturation levels above 93% on room air at rest, or an arterial blood gas oxygenation index exceeding 300 mmHg. Similarly, severe and critical cases, which share overlapping early warning indicators, clinical features, and treatment principles, were grouped together as the "severe/critical" (S/C) group. Key characteristics of patients in this group include a respiratory rate exceeding 30 breaths per minute, oxygen saturation levels of ≤93% on room air at rest, or an arterial blood gas oxygenation index of ≤300 mmHg (1 mmHg =0.133 kPa). In critical cases, patients may develop septic shock or multi-organ failure, necessitating intensive care unit (ICU) admission.

COVID-19 treatment

We adhere to the "Diagnosis and Treatment Program for Novel Coronavirus Infection (Trial Version 10)" (28) as our guideline for managing hospitalized LTRs. Our primary antiviral medication was naimatevir/ritonavir (Paxlovid), with occasional use of azvudine in select cases. The initiation of antiviral therapy was recommended within five days post-infection, preferably as early as possible. In cases where the oxygenation index declined to or below ≤300 mmHg, respiratory support strategies were administered by lung transplant specialists. These strategies predominantly included low-flow nasal cannula (LFNC), high-flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIMV), and invasive mechanical ventilation (IMV). Prone positioning and extracorporeal membrane oxygenation (ECMO) assistance, when necessary, were employed. In instances of pronounced inflammatory responses, lung transplant specialists prescribed medications such as methylprednisolone, dexamethasone, baricitinib, or tocilizumab based on the patient's clinical condition. Additionally, all LTRs received comprehensive supportive care tailored to the specific needs of their individual organ systems.

Non-hospitalized infected LTRs received symptomatic and supportive care, with an appropriate reduction in immunosuppressive intensity. No antiviral, anti-inflammatory, or respiratory support treatments were administered.

Statistical analyses

Data analysis was performed with SAS 9.4 statistical software. The measurement data conforming to the normal distribution were described by mean ± standard deviation (SD); the measurement data not conforming to the normal distribution are described by the median (interquartile range, IQR). Continuous variable data were compared between groups using analysis of variance or rank sum test. Count data were used to calculate constituent ratios, and Chi-squared test or exact probability method was used for comparison between groups. Pearson correlation was used for the correlation analysis between two continuous variables. Risk factors were analyzed by multivariate logistic

regression analysis. The test level was α=0.05 (normality test was α=0.01).

Results

Demographics and baseline characteristic

Between November 17, 2022, and May 1, 2023, 49 individuals remained uninfected and were excluded from further analysis. This left a final cohort of 178 infected LTRs, accounting for an infection rate of 78.4% (178/227). Hospitalization was required for 50% (89/178) of the patients. *Table 1* presented the baseline characteristics of 178 patients, highlighting the differences between hospitalized and non-hospitalized individuals. Notably, only 41 patients had received a COVID-19 vaccine, corresponding to a low vaccination rate of 23.0% (41/178) (*Figure 2*). Among 178 LTRs with COVID-19, the most common symptoms were dry cough (75.3%), fever (67.4%) and fatigue (61.8%), while less frequent symptoms included vomiting (13.5%), anosmia (9.0%), and ageusia (10.7%).

Compared with non hospitalized LTRs, hospitalized LTRs exhibited more severe symptoms, including dry cough, expectoration, chills, dyspnea and nausea (*Table 1*). Among the 89 hospitalized cases, 37 LTRs progressed to severe or critical disease (S/C group), accounting for 41.6% (37/89), while the remaining 52 patients (58.4%, 52/89) were classified as having mild or moderate disease (M/M group). As detailed in *Table 2*, there were no significant differences between the two groups in terms of age, gender, body mass index (BMI), type of transplantation, primary disease, baseline immunosuppressive regimen, or vaccination

Table 1 Baseline characteristics and clinical symptoms of 178 LTRs infected with Omicron variant

Variables	Total (n=178)	Hospitalized (n=89)	Non-hospitalized (n=89)	P value
Age, years, median (IQR)	63.0 (53.0–69.0)	65.0 (53.0–69.0)	63.0 (51.5–68.5)	0.45
Age category, years, n (%)				0.37
<65	94 (52.8)	44 (49.4)	50 (56.2)	
≥65	84 (47.2)	45 (50.6)	39 (43.8)	
Sex, male, n (%)	144 (80.9)	74 (83.1)	70 (78.7)	0.45
BMI, kg/m^2, mean (SD)	21.9 (3.7)	21.5 (3.7)	22.3 (3.6)	0.10
BMI category, kg/m^2, n (%)				0.09
<18.5	32 (18.0)	21 (23.6)	11 (12.4)	
18.5–23.9	94 (52.8)	47 (52.8)	47 (52.8)	
≥24	52 (29.2)	21 (23.6)	31 (34.8)	
Type of LT, n (%)				0.39
Single lung	64 (36.0)	35 (39.3)	29 (32.6)	
Double lung	114 (64.0)	54 (60.7)	60 (67.4)	
Indication for LT, n (%)				0.003*
Interstitial lung disease	132 (74.2)	75 (84.3)	57 (64.0)	
Obstructive pulmonary disease	26 (14.6)	6 (6.7)	20 (22.5)	
Pulmonary arterial hypertension	4 (2.2)	2 (2.2)	2 (2.2)	
Graft-*vs.*-host pulmonary disease	6 (3.4)	4 (4.5)	2 (2.2)	
Bronchiectasis and cystic fibrosis	2 (1.1)	0	2 (2.2)	
Others	8 (4.5)	2 (2.2)	6 (6.7)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total (n=178)	Hospitalized (n=89)	Non-hospitalized (n=89)	P value
Vaccination status, n (%)				0.32
Non-vaccinated	137 (77.0)	73 (82.0)	64 (71.9)	
1 dose	5 (2.8)	1 (1.1)	4 (4.5)	
2 doses	15 (8.4)	7 (7.9)	8 (9.0)	
3 doses	21 (11.8)	8 (9.0)	13 (14.6)	
Ongoing treatment before COVID-19 episode, n (%)				
Oral corticosteroids	177 (99.4)	89 (100.0)	88 (98.9)	0.99
Tacrolimus	173 (97.2)	85 (95.5)	88 (98.9)	0.37
Mycophenolate mofetil	155 (87.1)	73 (82.0)	82 (92.1)	0.04*
Sirolimus	2 (1.1)	2 (2.2)	0	0.49
Cyclosporine	3 (1.7)	2 (2.2)	1 (1.1)	0.99
Settings of COVID-19 acquisition, n (%)				<0.001*
Community-acquired	156 (87.6)	67 (75.3)	89 (100.0)	
Hospital-acquired	22 (12.4)	22 (24.7)	0	
Time from LT surgery, median (IQR), days	877.0 (431.7–1,413.5)	610.0 (289.0–1,215.5)	1,129.0 (715.0–1,495.5)	<0.001*
Time from last vaccination, median (IQR), days	451.0 (287.0–537.0)	451.0 (350.0–536.0)	442.0 (181.7–563.7)	0.87
Signs and symptoms of COVID-19, n (%)				
Fever	120 (67.4)	62 (69.7)	58 (65.2)	0.67
Dry cough	134 (75.3)	77 (86.5)	57 (64.0)	0.004*
Fatigue	110 (61.8)	60 (67.4)	50 (56.2)	0.27
Expectoration	91 (51.1)	58 (65.2)	33 (37.1)	0.001*
Stuffy or runny nose	40 (22.5)	23 (25.8)	17 (19.1)	0.37
Sore throat	56 (31.5)	30 (33.7)	26 (29.2)	0.75
Chills	31 (17.4)	22 (24.7)	9 (10.1)	0.02*
Myalgia	77 (43.3)	33 (37.1)	44 (49.4)	0.07
Dyspnea	56 (31.5)	36 (40.4)	20 (22.5)	0.02*
Headache	42 (23.6)	18 (20.2)	24 (27.0)	0.29
Nausea	38 (21.3)	26 (29.2)	12 (13.5)	0.02*
Diarrhea	32 (18.0)	21 (23.6)	11 (12.4)	0.08
Vomit	24 (13.5)	13 (14.6)	11 (12.4)	0.83
Anosmia	16 (9.0)	9 (10.1)	7 (7.9)	0.79
Ageusia	19 (10.7)	10 (11.2)	9 (10.1)	0.99

*, a statistically significant difference between the two groups. LTRs, lung transplant recipients; IQR, interquartile range; BMI, body mass index; SD, standard deviation; LT, lung transplant; COVID-19, coronavirus disease 2019.

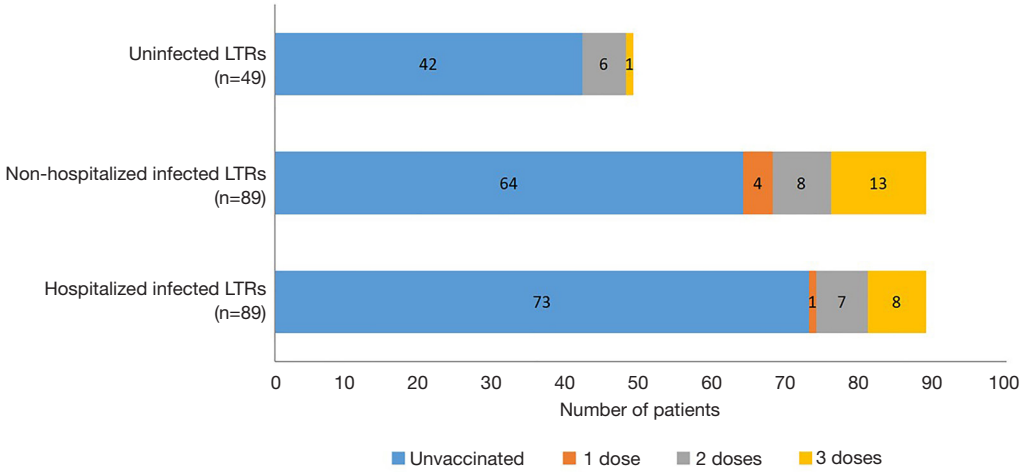

Figure 2 COVID-19 vaccination status of 49 uninfected LTRs and 178 infected LTRs. COVID-19, coronavirus disease 2019; LTRs, lung transplant recipients.

rates. The average time from COVID-19 onset to hospital admission was 11 days, with the S/C group exhibiting a significantly shorter duration compared to the M/M group (8 *vs.* 13 days, P=0.04). Additionally, significant differences were also noted regarding the time from COVID-19 onset to lung transplant surgery and the interval since the last vaccination.

Among the 89 hospitalized LTRs, 67 (75.3%, 67/89) had been discharged and 9 (10.1%, 9/89) remained hospitalized by the time of the last follow-up. However, 37 (41.6%, 37/89) were readmitted due to secondary infections and other reasons during the study period. No COVID-19 cases at our center were linked to suspected donor origins.

Characteristics of COVID-19

Table 3 provided a summary of clinical symptoms, laboratory and radiologic features observed in 89 hospitalized COVID-19 cases. Compared to the M/M group, the S/C group exhibited a higher incidence of fever (83.8% *vs.* 59.6%, P=0.02) and dyspnea (62.2% *vs.* 25.0%, P<0.001). In terms of laboratory tests, the S/C group demonstrated significantly higher white blood cell counts [7.88 *vs.* 5.58 ($\times10^9$/L), P=0.02], neutrophil counts [5.22 *vs.* 3.88 ($\times10^9$/L), P=0.02] and neutrophil-to-lymphocyte ratio (NLR) (5.40 *vs.* 4.35, P=0.04) within 48 hours of hospital admission, as well as C-reactive protein (CRP) (59.6 *vs.* 16.8 mg/L, P<0.001), Erythrocyte sedimentation rate (ESR) (45.5 *vs.* 22.5 mm/h, P=0.005), D-dimer (1.09 *vs.* 0.65 mg/L, P=0.01) and human brain natriuretic peptide (BNP) (193 *vs.* 110 pg/mL, P=0.02). Conversely, $CD4^+$ T lymphocyte counts (217 *vs.* 427 cells/μL, P=0.004) were lower in the S/C group. No significant differences were observed between the two groups regarding interleukin-6 (IL-6), serum ferritin, and procalcitonin (PCT). Chest computed tomography (CT) showed acute parenchymal abnormalities in 87.6% (78/89) hospitalized cases. The most common manifestation was ground-glass opacities (76.4%, 68/89), followed by consolidation (31.5%, 28/89). Compared with the M/M group, the imaging findings in the S/C group were significantly worse (all P<0.01).

Treatment

In terms of respiratory support, HFNC was the most widely employed method, accounting for 43.8% (39/89). Notably, 89.1% (33/37) of patients in the S/C group required HFNC, followed by NIMV, which was used in 51.4% (19/37) of cases. Additionally, 12.4% (11/89) of patients underwent prone position ventilation to improve oxygenation, all of whom were from the S/C group (*Table 4*).

Regardless of disease severity, approximately 80% of LTRs with COVID-19 underwent modifications to their baseline anti-rejection regimens, primarily through the reduction or discontinuation of calcineurin inhibitors (CNI) or mycophenolate mofetil (MMF). Additionally, around three-quarters of LTRs received Naimatevir/Ritonavir for antiviral treatment, with a significantly higher usage

Table 2 Demographics and baseline characteristics of 89 hospitalized LTRs by disease severity

Variables	Total	M/M group	S/C group	P value
Number, n (%)	89 (50.0)	52 (58.4)	37 (41.6)	–
Age, years, median (IQR)	65.0 (53.0–69.0)	63.0 (53.3–69.0)	65.0 (53.0–69.5)	0.64
Age category, years, n (%)				
<65	44 (49.4)	27 (51.9)	17 (45.9)	0.58
≥65	45 (50.6)	25 (48.1)	20 (54.1)	
Sex, male, n (%)	74 (83.1)	42 (80.8)	32 (86.5)	0.48
BMI, kg/m^2, mean (SD)	21.5 (3.7)	21.6 (3.9)	21.3 (3.3)	0.71
BMI category, kg/m^2, n (%)				0.27
<18.5	21 (23.6)	13 (25.0)	8 (21.6)	
18.5–23.9	47 (52.8)	24 (46.2)	23 (62.2)	
≥24	21 (23.6)	15 (28.8)	6 (16.2)	
Type of LT, n (%)				0.13
Single lung	35 (39.3)	17 (32.7)	18 (48.6)	
Double lung	54 (60.7)	35 (67.3)	19 (51.4)	
Indication for LT, n (%)				0.64
Interstitial lung disease	75 (84.2)	41 (78.8)	34 (91.9)	
Obstructive pulmonary disease	6 (6.7)	4 (7.7)	2 (5.4)	
Pulmonary arterial hypertension	2 (2.2)	2 (3.8)	0	
Graft-*vs.*-host pulmonary disease	4 (4.5)	3 (5.8)	1 (2.7)	
Bronchiectasis and cystic fibrosis	0	0	0	
Others	2 (2.2)	2 (3.8)	0	
Vaccination status, n (%)				0.95
Nonvaccinated	73 (82.0)	43 (82.7)	30 (81.1)	
1 dose of vaccine	1 (1.1)	1 (1.9)	0	
2 doses of vaccine	7 (7.9)	4 (7.7)	3 (8.1)	
3 doses of vaccine	8 (9.0)	4 (7.7)	4 (10.8)	
Ongoing treatment before COVID-19 episode, n (%)				
Oral corticosteroids	89 (100.0)	52 (100.0)	37 (100.0)	0.99
Tacrolimus	85 (95.5)	51 (98.1)	34 (91.9)	0.30
Mycophenolate mofetil	73 (82.0)	44 (84.6)	29 (78.4)	0.45
Sirolimus	2 (2.2)	1 (1.9)	1 (2.7)	0.99
Cyclosporine	2 (2.2)	0	2 (5.4)	0.17
Settings of COVID-19 acquisition, n (%)				0.67
Community-acquired	67 (75.3)	40 (76.9)	27 (73.0)	
Hospital-acquired	22 (24.7)	12 (23.1)	10 (27.0)	
Time from LT surgery, days, median (IQR)	610.0 (289.0–1,215.5)	524.5 (222.5–858.5)	769.0 (364.5–1,562.0)	0.03*
Time from last vaccination, days, median (IQR)	451.0 (350.0–536.0)	534.0 (426.5–593.0)	350.0 (287.0–451.0)	0.01*
Time from hospital admission, days, median (IQR)	11.0 (4.0–20.5)	13.0 (7.0–25.0)	8.0 (2.5–16.5)	0.04*

*, a statistically significant difference between the two groups. LTRs, lung transplant recipients; M/M, mild/moderate disease; S/C, severe/critical disease; IQR, interquartile range; BMI, body mass index; SD, standard deviation; LT, lung transplant; COVID-19, coronavirus disease 2019.

Table 3 Clinical features, laboratory and radiologic findings of 89 hospitalized LTRs by disease severity

Variables	Total (n=89)	M/M group (n=52)	S/C group (n=37)	P value
Clinical features				
Signs and symptoms, n (%)				
Fever	62 (69.7)	31 (59.6)	31 (83.8)	0.02*
Dry cough	77 (86.5)	46 (88.5)	31 (83.8)	0.55
Fatigue	60 (67.4)	36 (69.2)	24 (64.9)	0.67
Expectoration	58 (65.2)	33 (63.5)	25 (67.6)	0.69
Stuffy or runny nose	23 (25.8)	15 (28.8)	8 (21.6)	0.44
Sore throat	30 (33.7)	16 (30.8)	14 (37.8)	0.49
Chills	22 (24.7)	10 (19.2)	12 (32.4)	0.22
Myalgia	33 (37.1)	18 (34.6)	15 (40.5)	0.66
Dyspnea	36 (40.4)	13 (25.0)	23 (62.2)	<0.001*
Headache	18 (20.2)	12 (23.1)	6 (16.2)	0.44
Nausea	26 (29.2)	18 (34.6)	8 (21.6)	0.18
Diarrhea	21 (23.6)	14 (26.9)	7 (18.9)	0.45
Vomit	13 (14.6)	7 (13.5)	6 (16.2)	0.72
Anosmia	9 (10.1)	5 (9.6)	4 (10.8)	0.99
Ageusia	10 (11.2)	7 (13.5)	3 (8.1)	0.51
Chest CT-scan findings				
Radiological pattern, n (%)				
Ground-glass opacities	68 (76.4)	34 (65.4)	34 (91.9)	0.004*
Consolidations	28 (31.5)	9 (17.3)	19 (51.4)	0.001*
Both	18 (20.2)	2 (3.8)	16 (43.2)	<0.001*
Laboratory findings				
White cell count, median (IQR), $\times10^9$/L	6.22 (4.47–9.09)	5.58 (4.43–7.72)	7.88 (4.88–10.89)	0.02*
<4, n (%)	15 (16.9)	10 (19.2)	5 (13.5)	0.03*
≥4 to ≤10, n (%)	55 (61.8)	36 (69.2)	19 (51.4)	
>10, n (%)	19 (21.3)	6 (11.5)	13 (35.1)	
Neutrophils count, median (IQR), $\times10^9$/L	4.63 (3.01–7.75)	3.88 (2.73–7.01)	5.22 (3.84–9.67)	0.02*
>3.74, n (%)	58 (65.2)	29 (55.8)	29 (78.4)	0.03*
≤3.74, n (%)	31 (34.8)	23 (44.2)	8 (21.6)	
Lymphocyte count, median (IQR), $\times10^9$/L	0.87 (0.63–1.31)	0.89 (0.61–1.35)	0.86 (0.64–1.28)	0.67
<0.8, n (%)	38 (42.7)	22 (42.3)	16 (43.2)	0.73
≥0.8, n (%)	51 (57.3)	30 (57.7)	21 (56.8)	

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Total (n=89)	M/M group (n=52)	S/C group (n=37)	P value
NLR, median (IQR)	4.80 (2.80–10.60)	4.35 (2.33–7.93)	5.40 (3.70–14.4)	0.04*
<5, n (%)	42 (47.2)	26 (50.0)	16 (43.2)	0.09
≥5 to ≤10, n (%)	24 (27.0)	17 (32.7)	7 (18.9)	
>10, n (%)	23 (25.8)	9 (17.3)	14 (37.8)	
CRP, mg/L, median (IQR)	34.4 (10.7–87.9)	16.8 (3.1–49.9)	59.6 (35.3–136.1)	<0.001*
PCT, ng/mL, median (IQR)	0.10 (0.10–0.17)	0.10 (0.10–0.13)	0.10 (0.10–0.28)	0.14
ESR, mm/h, median (IQR)	33.0 (14.3–54.3)	22.5 (12.0–43.2)	45.5 (24.8–66.3)	0.005*
D-dimer, mg/L, median (IQR)	0.79 (0.46–1.69)	0.65 (0.39–1.31)	1.09 (0.66–2.83)	0.01*
Serum ferritin, μg/L, median (IQR)	332.7 (164.0–562.2)	251.7 (153.1–562.2)	372.7 (194.1–617.5)	0.28
IL-6, pg/mL, median (IQR)	11.7 (5.3–55.6)	11.4 (4.2–34.5)	19.2 (5.8–77.6)	0.12
$CD3^+$T lymphocyte count, /μL, median (IQR)	807.0 (503.8–1,225.0)	962.0 (655.0–1,409.0)	577.0 (336.0–936.0)	0.005*
$CD4^+$T lymphocyte count, /μL, median (IQR)	353.5 (177.5–621.7)	427.0 (271.0–671.0)	217.0 (83.0–455.0)	0.004*
$CD8^+$T lymphocyte count, /μL, median (IQR)	393.0 (227.0–572.0)	421.5 (236.0–604.3)	331.0 (185.0–529.0)	0.11
$CD19^+$B lymphocyte count, /μL, median (IQR)	56.0 (25.0–137.0)	66.0 (26.0–231.0)	38.0 (18.0–77.0)	0.05
NK cell count, /μL, median (IQR)	155.0 (78.0–319.0)	154.5 (82.0–301.8)	210.0 (57.0–357.0)	0.99
IgG, mg/dL, mean (SD)	951.9 (282.6)	916.0 (230.0)	1,008.0 (347.2)	0.58
IgA, mg/dL, median (IQR)	158.0 (106.0–221.0)	152.0 (101.0–204.0)	174.0 (114.5–249.5)	0.13
IgM, mg/dL, median (IQR)	69.9 (50.1–87.7)	69.8 (51.7–91.5)	70.0 (45.2–85.8)	0.79
C3, mg/dL, mean (SD)	89.3 (19.7)	88.9 (19.4)	90.0 (20.5)	0.67
C4, mg/dL, median (IQR)	26.4 (21.1–32.8)	26.1 (19.6–31.6)	27.1 (23.5–35.9)	0.16
cTnI, ng/mL, median (IQR)	0.012 (0.007–0.019)	0.012 (0.006–0.017)	0.012 (0.009–0.022)	0.24
BNP, pg/mL, median (IQR)	151.0 (53.8–271.5)	110.0 (47.0–194.0)	193.0 (99.0–363.0)	0.02*
Serum creatinine, μmol/L, median (IQR)	104.2 (76.9–136.5)	103.8 (76.9–123.2)	118.6 (74.9–149.3)	0.26
ALT, IU/L, median (IQR)	17.5 (13.3–31.0)	15.5 (13.0–26.0)	20.5 (14.0–34.7)	0.10
AST, IU/L, median (IQR)	23.0 (19.0–30.7)	20.5 (16.3–27.8)	29.5 (22.0–37.5)	0.10

*, a statistically significant difference between the two groups. LTRs, lung transplant recipients; M/M, mild/moderate disease; S/C, severe/critical disease; CT, computed tomography; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; NK cell, natural killer cell; SD, standard deviation; BNP, human brain natriuretic peptide; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

observed in the S/C group compared to the M/M group (94.6% *vs.* 61.5%, P<0.001). Anti-inflammatory treatments were administered based on clinical assessments of the inflammatory response, including the individualized use of glucocorticoids. Notably, in the S/C group, a higher proportion of patients received methylprednisolone (45.9% *vs.* 9.6%, P<0.001) or baricitinib (18.9% *vs.* 3.8%, P=0.03) (*Table 4*).

Table 4 Treatments and outcomes of 89 hospitalized LTRs by disease severity

Variables	Total (n=89)	M/M group (n=52)	S/C group (n=37)	P value
Treatments for COVID-19 disease				
PaO_2/FiO_2, median (IQR), mmHg	314 (226–365)	350 (320–399)	212 (137–256)	<0.001*
Types of COVID-19 disease, n (%)				<0.001*
Mild	13 (14.6)	13 (25.0)	–	
Moderate	39 (43.8)	39 (75.0)	–	
Severe	29 (32.6)	–	29 (78.4)	
Critical	8 (9.0)	–	8 (21.6)	
Respiratory failure management, n (%)				
None	28 (31.5)	28 (53.8)	0	<0.001*
LFNC	24 (27.0)	18 (34.6)	6 (16.2)	0.09
HFNC	39 (43.8)	6 (11.5)	33 (89.1)	<0.001*
NIMV	23 (25.8)	4 (7.7)	19 (51.4)	<0.001*
Intubation	13 (14.6)	0	13 (35.1)	<0.001*
Tracheotomy	7 (7.9)	0	7 (18.9)	0.02*
ECMO	2 (2.2)	0	2 (5.4)	0.17
Prone positioning	11 (12.4)	0	11 (29.7)	<0.001*
Anti-rejection regimen adjustment, n (%)				0.14
Down-regulation	73 (82.0)	40 (76.9)	33 (89.2)	
Maintain original dose	16 (18.0)	12 (23.1)	4 (10.8)	
Anti-inflammatory management, n (%)				
Methylprednisolone	22 (24.7)	5 (9.6)	17 (45.9)	<0.001*
Dexamethasone	11 (12.4)	6 (11.5)	5 (13.5)	0.99
Baricitinib	9 (10.1)	2 (3.8)	7 (18.9)	0.03*
Tocilizumab	1 (1.1)	0	1 (2.7)	0.42
Antiviral drugs application, n (%)				<0.001*
Naimatevir/ritonavir	67 (75.3)	32 (61.5)	35 (94.6)	
Azvudine	2 (2.2)	2 (3.8)	0	
None	20 (22.5)	18 (34.6)	2 (5.4)	
Complications				
Infection complication, n (%)				
Lung bacterial infection	45 (50.6)	20 (38.5)	25 (67.6)	0.006*
Lung fungal infection	47 (52.8)	20 (38.5)	27 (73.0)	0.001*
Lung other viral infection	11 (12.4)	6 (11.5)	5 (13.5)	0.99
Extrapulmonary infection	9 (10.1)	3 (5.8)	6 (16.2)	0.15
DVT	15 (16.9)	8 (15.4)	7 (18.9)	0.70
Outcomes				
Length of hospital stay, median (IQR), days	16.0 (9.5–25.5)	13.0 (8.0–19.0)	19.0 (10.0–26.8)	0.01*
Duration of nucleic acid positive, median (IQR), days	25.0 (19.0–33.0)	28.0 (16.0–37.0)	25.0 (20.0–31.5)	0.62
Outcomes, n (%)				0.02*
Alive	76 (85.4)	52 (100.0)	24 (64.9)	
Death	13 (14.6)	0	13 (35.1)	

*, a statistically significant difference between the two groups. LTRs, lung transplant recipients; M/M, mild/moderate disease; S/C, severe/critical disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; LFNC, low-flow nasal cannula; HFNC, high-flow nasal cannula; NIMV, non-invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation; DVT, deep vein thrombosis.

Complications and outcomes

LTRs prominently experienced combined pulmonary infections after COVID-19, especially in the S/C group (*Table 4*). Compared with the M/M group, a substantial 67.6% of patients in the S/C group had combined pulmonary bacterial infections (67.6% *vs.* 38.5%, P=0.006), while 73.0% exhibited combined pulmonary fungal infections (73.0% *vs.* 38.5%, P=0.001). Additionally, 10.1% (9/89) of patients experienced extrapulmonary infections, such as periorbital soft tissue infections, acute sinusitis, or urinary tract infections. There was no significant difference between the S/C and M/M groups regarding the occurrence of deep vein thrombosis (DVT).

As of submission, no deaths were reported among the 89 non-hospitalized patients. However, 13 of the 89 hospitalized LTRs succumbed to COVID-19 or its complications, resulting in an overall mortality rate of 7.3% (13/178). Notably, no deaths occurred in the M/M group, whereas the S/C group experienced a significantly higher mortality rate of 35.1% (13/37, P=0.02). The primary causes of death were respiratory failure and multiple organ dysfunction caused by COVID-19. Additionally, the average hospital stay in the S/C group was 19 days (IQR: 10.0–26.8 days), significantly longer than the 13.0 days (IQR: 8.0–19.0 days) observed in the M/M group (P=0.01).

Among the 13 patients who died, the survival time following a confirmed COVID-19 diagnosis ranged from 11 to 87 days, with a median of 19 days (IQR: 14–38.5 days). Ten received treatment in the ICU, while 3 declined ICU admission based on personal preferences. The time between hospital admission and ICU transfer varied widely, ranging from 0 to 86 days, with a median of 4.5 days (IQR: 0–6.5 days). ICU stays lasted between 1 and 27 days, with an average duration of 8.8 days.

Risk factors for severe disease and death

In this study, no patients experienced acute cardiovascular events due to COVID-19. Correlation analysis revealed a strong positive correlation between CRP and cardiac troponin I (cTnI), with a correlation coefficient of r=0.710 (P<0.001, N=86). Moderate correlations were observed between CRP and serum ferritin, and between CRP and PCT, with correlation coefficients of r=0.562 (P<0.001, N=50), r=0.524 (P<0.001, N=87), respectively.

Multivariate logistic regression analysis revealed that CRP >41.8 mg/L, combined pulmonary fungal infection, and interstitial lung disease (ILD) as the primary pulmonary disease were high-risk factors for progressing to a severe phenotype, with odds ratios (ORs) of 4.23 [95% confidence interval (CI):1.68–11.23], 4.76 (95% CI: 1.59–15.64), and 5.13 (95% CI: 1.19–29.17), respectively (*Table 5*).

To identify biomarkers for predicting mortality risk in LTRs with COVID-19, we analyzed clinical indicators using receiver operating characteristic (ROC) curves, including age, BMI, white blood cell count, neutrophils, $CD4^+$ and $CD8^+$ T lymphocytes, NLR, ESR, CRP, PCT, IL-6, D-dimer, cTnI, BNP and serum ferritin. Among these, $CD4^+$ T lymphocyte count had the highest area under the curve (AUC > 0.8), indicating its potential as a strong mortality predictor. At a cutoff of 404 cells/μL, $CD4^+$ T lymphocyte count yielded a sensitivity of 0.509 and specificity of 0.999, with an AUC of 0.806 (95% CI: 0.678–0.934, P=0.003) (*Figure 3*).

Discussion

In the pre-Omicron era, LTRs infected with earlier SARS-CoV-2 variants were reported to have a notably high hospitalization rate exceeding 80%, with mortality ranging from 14.3% to 43% (21,29,30). However, the Omicron variant, while more transmissible and immune-evasive, has been shown to be less pathogenic and lethal than previous VOCs (3-5). We focused on characterizing the clinical presentation and outcomes of Omicron infection in LTRs. Our study found that 78.4% (178/227) of LTRs were infected with Omicron. Of these, 50% (89/178) required hospitalization, 20.8% (37/178) developed severe disease, and 7.8% (13/178) succumbed to the infection. Despite a higher proportion of patients receiving antiviral treatment (94.6% *vs.* 65.3%, P<0.001), the S/C group had a striking mortality rate of 35.1% (13/37) and required more intensive respiratory support. The primary causes of death were septic shock originating from the lungs (9/13), followed by infections of the biliary tract (2/13), intestine (1/13), and bloodstream (1/13). These findings underscore that, even in the context of the less virulent Omicron variant, LTRs remain at significant risk for poor outcomes. The increased transmissibility of Omicron does not mitigate the considerable threat it poses to this vulnerable population.

Consistent with previous studies (21,31,32), the primary symptoms observed in LTRs following Omicron infection were dry cough (75.3%), fever (67.4%) and fatigue (61.8%). Notably, compared to the M/M group, the S/C group had a significantly higher incidence of fever (83.8% *vs.*

Table 5 Multivariate logistic regression analysis for severe illness

Independent variable	OR (95% CI)	P value
Sex (female, yes/no)	0.83 (0.22–2.84)	0.78
Age (>65 years)	1.18 (0.45–3.12)	0.73
BMI (<18.5 kg/m^2)	0.92 (0.27–3.12)	0.89
BMI (≥24 kg/m^2)	0.67 (0.19–2.20)	0.51
No vaccinated (yes/no)	1.28 (0.37–4.35)	0.69
White cell count (<4×10^9/L)	0.90 (0.19–3.81)	0.88
White cell count (>10×10^9/L)	3.32 (1.02–11.89)	0.05
Lymphocyte count (<0.8×10^9/L)	1.22 (0.47–3.26)	0.69
Neutrophil count (>3.74×10^9/L)	2.04 (0.67–6.58)	0.22
NLR (>10)	2.40 (0.55–11.54)	0.26
Indication for LT (ILD, yes/no)	5.13 (1.19–29.17)	0.04*
Lung bacterial infection (yes/no)	2.32 (0.85–6.47)	0.10
Lung fungal infection (yes/no)	4.76 (1.59–15.64)	0.003*
CRP (>41.8 mg/L)	4.23 (1.68–11.23)	0.007*
ESR (>20 mm/h)	4.57 (1.04–25.69)	0.06
IL-6 (>32.1 pg/mL)	2.45 (0.68–9.42)	0.18
Ferritin (>300 μg/L)	3.15 (0.76–14.41)	0.12
D-dimer (>1 mg/L)	1.87 (0.71–5.00)	0.20
BNP (>100 pg/mL)	2.04 (0.72–6.16)	0.19
PCT (>0.5 ng/mL)	0.87 (0.14–4.88)	0.87
CD4$^+$ T cell count (>400/μL)	0.70 (0.18–2.69)	0.59
CD8$^+$ T cell count (>270/μL)	2.54 (0.63–12.29)	0.21
CD19$^+$ B cell count (>90/μL)	0.55 (0.13–2.15)	0.39
NK cell count (>135/μL)	0.82 (0.25–2.71)	0.75

*, a statistically significant difference between the two groups. The model was adjusted for sex, age, BMI, vaccination status, CRP and lymphocyte count. OR, odds ratio; CI, confidence interval; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; LT, lung transplant; ILD, interstitial lung disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; BNP, human brain natriuretic peptide; PCT, procalcitonin; NK cell, natural killer cell.

59.6%, P=0.02) and dyspnea (62.2% *vs.* 25.0%, P <0.001). Chest radiography also showed that the imaging findings in the S/C group were significantly worse (all P<0.01). Obviously, LTRs in the S/C group had a worse respiratory status and chest CT performance on admission. The COVID-19 vaccination rate in our study was only 23.0%

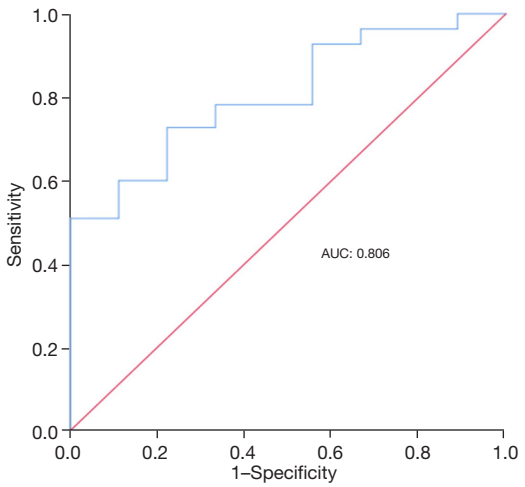

Figure 3 ROC curve of CD4$^+$ T lymphocyte count for predicting mortality risk in LTRs with COVID-19. AUC, area under the curve; ROC, receiver operating characteristic; LTRs, lung transplant recipients; COVID-19, coronavirus disease 2019.

(41/178). Previous reports have shown that the post-vaccination humoral response is significantly inhibited by immunosuppressive therapy in SOT recipients (33). As a result, vaccination likely had minimal effect in preventing COVID-19 in our cohort of LTRs, particularly considering that they contracted the virus at least one year after their last vaccination.

As widely reported, COVID-19 infection is associated with lymphocytemia (34), and T lymphocyte subsets, particularly CD4$^+$ T cells, can serve as important predictive markers for disease progression from mild to severe stages (35,36). Moreover, an elevated neutrophil count has been linked to worse clinical outcomes in hospitalized COVID-19 patients, with a threshold of 3.74×10^9/L identified as a critical marker for severe disease, showing 100% sensitivity and 78.5% specificity (37,38). In our study, patients in the S/C group had significantly lower CD3$^+$ and CD4$^+$ T lymphocyte counts, along with higher white blood cell counts, neutrophil levels, and NLR. ROC curve analysis revealed that a CD4$^+$ T lymphocyte count of <404 cells/μL may be a strong predictor of mortality in LTRs with COVID-19. These biomarkers, easily measured at the time of hospital admission, can aid in the early identification of high-risk patients. Clinicians should closely monitor recipients exhibiting these characteristics, as they may indicate severe disease progression and poor prognosis, helping to guide timely interventions and personalized

management.

Recent studies have demonstrated that individuals with severe COVID-19 exhibit significantly elevated levels of inflammatory markers such as CRP, D-dimer, ferritin, and IL-6, when compared to those with moderate disease (29,39,40). The dynamic changes in these markers, particularly CRP, can provide critical insights into disease progression and clinical prognosis (40,41). In our study, the S/C group showed significantly higher levels of CRP (59.6 *vs.* 16.8 mg/L, P<0.001), ESR (45.5 *vs.* 22.5 mm/h, P=0.005), and D-dimer (1.09 *vs.* 0.65 mg/L, P=0.01), reflecting a more intense systemic inflammatory response. Multivariate logistic regression analysis further revealed that CRP levels exceeding 41.8 mg/L were strongly associated with progression to severe disease in LTRs (*Table 5*). These findings are consistent with previous studies, which have established CRP as a reliable marker for identifying patients at high risk for poor outcomes and complications (38,39). Therefore, timely and regular monitoring of CRP levels in LTRs can serve as an early warning system for clinicians, enabling more accurate risk stratification and prompt intervention. In our study, the IL-6 level in the S/C group was 19.2 pg/mL, slightly higher than 11.4 pg/mL in the M/M group, but this difference was not statistically significant (P=0.12). This could be due to various factors influencing IL-6 levels, including viral strain, load, baseline immune status, and underlying lung disease. Additionally, severe cases may show no significant IL-6 increase due to immune suppression or immune escape mechanisms. The small sample size could also contribute to potential bias and limit the ability to detect statistically significant differences.

COVID-19 patients are at high risk of secondary bacterial, fungal, and viral infections (42-46). In non-immunosuppressed individuals, bacterial co-infections are rare, occurring in only 3.1% of COVID-19 cases (45). Even among critically ill non-transplant patients, invasive pulmonary fungal infections are reported in just 4.8% (46). In contrast, our study found a significantly higher incidence of COVID-19-associated pulmonary bacterial (50.6%) and fungal (52.8%) infections in immunosuppressed LTRs. In the S/C group, the rates of combined pulmonary bacterial (67.6% *vs.* 38.5%, P=0.006) and fungal infections (73.0% *vs.* 38.5%, P=0.001) were nearly twice those in the M/M group, which has highlighted the increased risk of infections in immunosuppressed patients. Our analysis also identified combined pulmonary fungal infection as a significant risk factor for severe disease progression in LTRs (OR: 4.76, 95% CI: 1.59–15.64, P=0.003), contributing to higher mortality in the S/C group. These findings are consistent with prior research (46). This heightened susceptibility is likely due to factors such as immune dysregulation, immunosuppressive therapy, and direct lung injury (47). Given the high risk of fungal infections in LTRs with COVID-19, early identification and targeted management of these infections are critical for improving outcomes in this vulnerable population.

Surprisingly, multivariate logistic regression revealed that ILD as the primary disease was a significant risk factor for developing severe COVID-19, with an OR of 5.13 (95% CI: 1.19–29.17, P=0.04). Previous studies have shown that ILD patients are more vulnerable to COVID-19, with a higher likelihood of respiratory failure and death compared to non-ILD patients (48-52). The risk of severe COVID-19 is substantially higher in ILD patients (adjusted OR: 2.23, 95% CI: 1.24–4.01), with idiopathic pulmonary fibrosis presenting the greatest risk (adjusted OR: 14.82, 95% CI: 3.96–63.74) (48). Interestingly, even after lung transplantation, LTRs with a history of ILD as their primary lung disease faced approximately five times the risk of severe COVID-19 compared to non-ILD patients. While the exact mechanisms remain unclear, this may be due to the immune dysregulation and inflammation inherent in ILD, which may worsen during SARS-CoV-2 infection. Conditions like chronic obstructive pulmonary disease, bronchiectasis, and pulmonary hypertension typically involve less pronounced immune-related pathophysiology, suggesting that ILD's unique immune response could contribute to worse outcomes during infection. These findings highlight the need for heightened attention and early intervention in LTRs with ILD to reduce the risk of severe COVID-19 progression.

This study has several limitations. First, as a single-center, retrospective study, the findings may not be fully generalizable. Second, the lack of a control group, such as non-immunocompromised individuals or non-pulmonary SOT recipients, limits direct comparisons of COVID-19 outcomes. Lastly, the absence of long-term follow-up, including assessments of lung graft function and clinical outcomes, highlights the need for further investigation into these aspects.

Conclusions

LTRs displayed an increased vulnerability to combined lung bacterial or fungal infections following SARS-CoV-2 infection. CRP >41.8 mg/L, ILD as primary disease,

and combined pulmonary fungal infection are high-risk factors for developing severe disease. Furthermore, $CD4^+$ T lymphocyte count may serve as a predictor of mortality risk in LTRs with COVID-19. This study highlights the importance of dynamic monitoring and prompt intervention in the management of LTRs with COVID-19, especially given the unique challenges presented by the Omicron variant.

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None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1314/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1314/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of China-Japan Friendship Hospital (No. 2022-KY-148) and informed consent was taken from all the patients.

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