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Short Report

Viral rebound and safety of nirmatrelvir/ritonavir for lung-transplant recipients infected with SARS-CoV-2

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ABSTRACT

Data on the viral rebound and safety of nirmatrelvir/ritonavir in lung transplant (LTx) recipients are limited. The study prospectively followed four LTx recipients. Clinical characteristics, viral RNA dynamic in throat swabs, and tacrolimus blood concentration were monitored regularly. All four LTx recipients, aged 35–74 years, were not vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). They got coronavirus disease 2019 (COVID-19) after more than one week of admission during the era of Omicron. All cases received nirmatrelvir/ritonavir (NM/r) within two days of infection, and the relative viral RNA copies dropped quickly. Viral load rebound was observed in all four cases after discontinuation of the first five days of NM/r treatment. Three of them received another 5-days antiviral therapy with NM/r. The duration of positive viral PCR testing was 25-28 days. None of them progressed into severe or critical COVID-19. Tacrolimus was stopped 12 h before NM/r and held during the 5-day course of antiviral therapy. Blood concentration of tacrolimus were maintained at a baseline level during these five days. Tacrolimus was re-initiated at its baseline daily dose 3-4 days after NM/r therapy. However, during the second round of antiviral therapy with NM/r, the concentration of tacrolimus fluctuated wildly. In conclusion, the 5-day course of NM/r treatment was not sufficient for LTx recipients and the viral rebound was common. More data are needed to clarify whether LTx recipients with SARS-CoV-2 viral rebound could benefit from additional treatment with NM/r.

1. Introduction

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2020, it has continued evolving into multiple subvariants. BA.5.2.1.7 (BF.7), a descendant of the Omicron sublineage BA.5, has recently been recognized as the primary variant circulating in Beijing, causing many infections [1]. Studies have revealed that the omicron variant of SARS-CoV-2 is more transmissible but less severe than previous variants, including the alpha, gamma, and delta variants [2–4]. However, the intrinsic severity, even between subvariants of omicron, showed a difference, and a recent research revealed that compared with BA.2 infections, patients infected with BA.5 had a higher risk of hospitalization[5].

Most patients infected with omicron presented with cough, expectoration, nasal congestion, and runny nose [6]. However, some progressed into pneumonia and even respiratory failure, especially in vulnerable groups such as those aged over 50 years, obese, immunocompromised, and with underlying diseases [7]. The overall mortality of solid organ transplant recipients infected with SARS-CoV-2 was 18.6%[8].

As one of the most effective methods to improve the outcome of patients infected with SARS-CoV-2, antiviral drugs including nirmatrelvir/ritonavir (NM/r, 300/100 mg), remdesivir, molnupiravir have been recommended for patients with high risk of hospitalization [9].

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As an oral protease inhibitor, NM/r can block viral replication by inhibiting the major protease of SARS-CoV-2, M^{PRO} [10]. Ritonavir, a strong cytochrome P450 (CYP) 3A4 inhibitor, is co-administrated to increase nirmatrelvir concentration. One real-world study revealed that NM/r was superior to molnupiravir in reducing the risk of hospitalization[11]. Nevertheless, virologic and symptomatic rebound after both NM/r and monulpiravir treatment has recently been reported [12]. Also, great concern exists about the safety of NM/r, which interacts with a series of CYP3A-dependent drugs, including cyclosporine, tacrolimus, and the mTOR inhibitors.

Lung transplant (LTx) recipients with weaker antiviral immune responses have been suggested to have prolonged viral shedding. Data regarding the efficacy and safety of NM/r in these patients are limited. This study reported the clinical characteristics and viral dynamics of four LTx cases infected with omicron and the efficacy and safety of NM/r in these patients.

2. Materials and methods

The study prospectively followed four LTx recipients who got infected with SARS-Cov-2 during hospitalization for complications of lung transplantation. Clinical characteristics were recorded.

Throat swabs were collected daily for all the recipients to test for SARS-CoV-2 after admission.

Viral RNA in oropharyngeal swabs was detected with the Novel Coronavirus (2019-nCoV) Nucleic Acid Detection Kit (PCR-Fluorescence Probing) from Biogerm. In brief, RNA was extracted from clinical samples with the MagNA Pure 96 system, detected and quantified by Cobasz480 qPCR (Roche), with the use of LightMix Modular SARS-CoV-2 (COVID19) assays (TIB MOBIOL). ORF1ab and N gene of SARS-CoV-2 were tested as target genes, and the RNase P gene was detected as endogenous control. The limit of detection was 150 copies per ml. ΔCt is the difference in Ct values for the ORF1ab or N gene of SARS-CoV-2 and the RNase P gene.

3. Results

3.1. Clinical characteristics of the four LTx recipients infected with SARS-CoV-2

All four recipients were male, aged 35 to 74 years. One had received a single lung transplantation nearly two years ago. The other three had received bilateral lung transplantation (Table 1). None of them have been vaccinated against SARS-CoV-2. All recipients were hospitalized for complications of lung transplantation. Three were hospitalized due to bronchial stenosis, and one was for chronic lung allograft dysfunction (Table 1). During their hospitalization, throat swabs were collected daily for all the recipients to test for SARS-CoV-2 via RT-PCR method according to the hospital regulation (Fig. 1). The four recipients tested positive for SARS-CoV-2 after more than one week of hospitalization. Three of them presented with fever. Progressively worsening fatigue, sore throat, nasal congestion, and diarrhea were not typical for all. No viral pneumonia was observed in any of the four recipients (Fig. 2).

3.2. Prolonged presence of viral RNA in throat swabs of LTx patients though with early NM/r therapy

Antiviral treatment was initiated within two days of positive viral PCR testing, and NM/r (300/100 mg) was taken twice daily for five consecutive days in all four recipients. All cases resolved rapidly, and the relative viral RNA copies decreased significantly. However, viral shedding rebounded in all four recipients within four days after stopping the first 5-day NM/r therapy, and two of them represented fever and fatigue (Fig. 3). Three of these recipients rapidly declined viral load after receiving a second 5-day course of NM/r for antiviral therapy. Although the viral load rebounded to a high level, Patient 1 did not present with any symptoms and did not agree to a second-course antiviral treatment, but he also recovered gradually. The dura-

Table 1
Clinical characteristics of the four LTx recipients infected with SARS-CoV-2.

Variable	Patient 1	Patient 2	Patient 3	Patient 4
Age-yr	50	74	54	35
Sex	Male	Male	Male	Male
Underlying disease for LT	SS-ILD	SS-ILD	Idiopathic pulmonary fibrosis	anti-synthetase syndrome
Procedure type	Bilateral	Single	Bilateral	Bilateral
Status of the graft	Bronchial Stenosis	Restrictive allograft syndrome	Bronchial Stenosis	Bronchial Stenosis
Immunosuppressive Drugs before SARS-CoV-2 infection	Tacrolimus 2 mg + 1.5 mg; Prednisone 15 mg qd; MMF 500 mg q12h	Tacrolimus 1 mg q12h; Prednisone 15 mg qd	Tacrolimus 1.5 mg q12h; Prednisone 10 mg qd; MMF 500 mg + 250 mg	Tacrolimus 1.5 mg + 1 mg; Prednisone 10 mg qd; EC-MPS 360 mg + 180 mg
Immunosuppressive drugs after SARS-CoV-2 infection*	Prednisone 15 mg qd; MMF 500 mg q12h D1-17, 250 mg q12h D18-27	Prednisone 15 mg qd	Prednisone 10 mg qd; MMF stopped D2-10, 250 mg q12h D11-27	Prednisone 10 mg qd; EC-MPS 360 mg + 180 mg
Azithromycin	No	250 mg orally for 5 days per week	No	No
Sulfonamide	Yes	Yes	Yes	Yes
comorbidities	Reflux esophagitis, Gastroparesis	Type 2 diabetes, Hypertension	Type 2 diabetes, Coronary atherosclerotic heart disease, Hepatitis B, Hypothyroidism, Renal insufficiency, Depression	Kidney stones
Lab information on the day of infection				
White-cell count - 10^9/L	4.23	14.68	4.59	9.49
Lymphocyte count - 10^9/L	1.13	2.87	1.22	1.52
Platelet count - 10^9/L	216	316	127	378
CRP - mg/L	31.02	28.97	6.46	9.77
PCT- ng/mL	<0.1	0.12	0.12	0.18
Fibrinogen - mg/dL	4.19	6.72	2.47	3.63
d-dimer - ng/mL	2.64	2.14	1.23	0.35

Abbreviations: LT, lung transplant; SS-ILD, Sjögren's syndrome-related interstitial lung disease; MMF, mycophenolate mofetil; EC-MPS, Enteric-coated Mycophenolate Sodium; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
* Immunosuppressive drugs except for tacrolimus after SARS-CoV-2 infection.

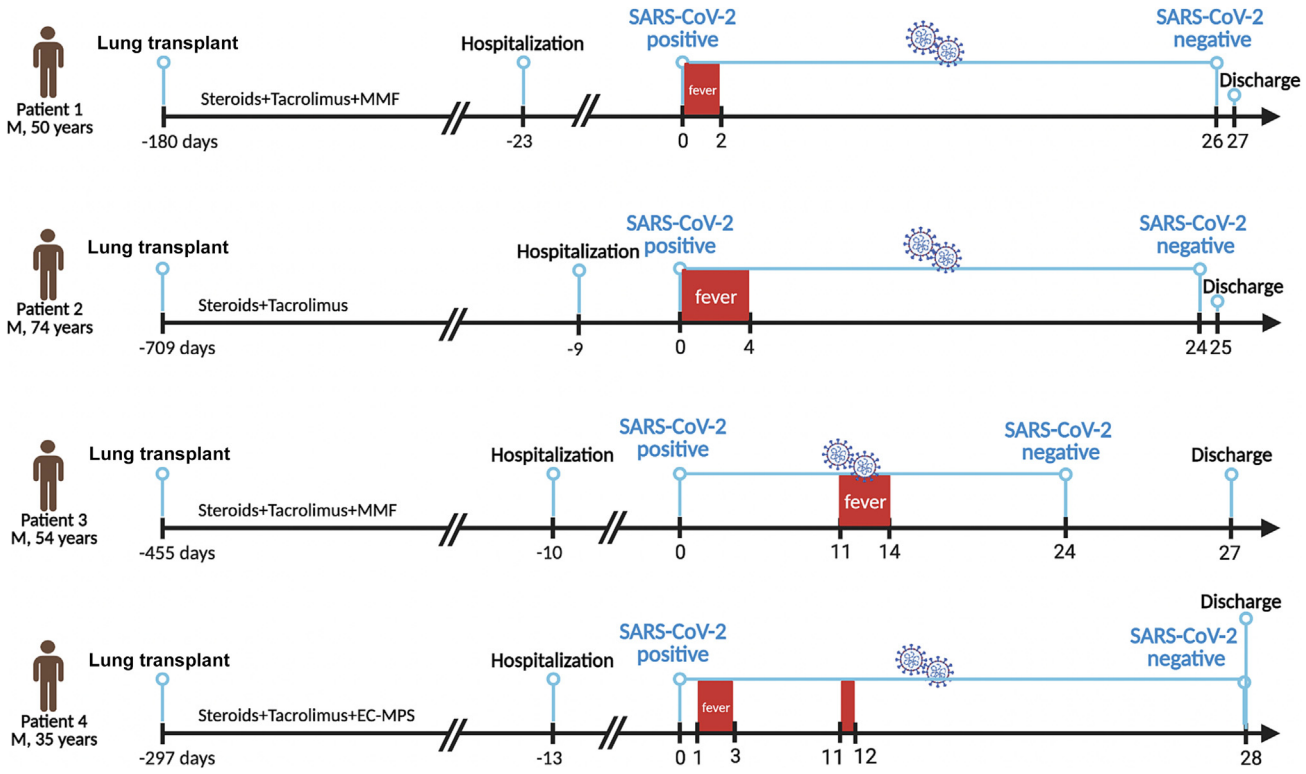

Fig. 1. Disease course of the four LTx recipients infected with SARS-CoV-2. Abbreviations: LT, lung transplant; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

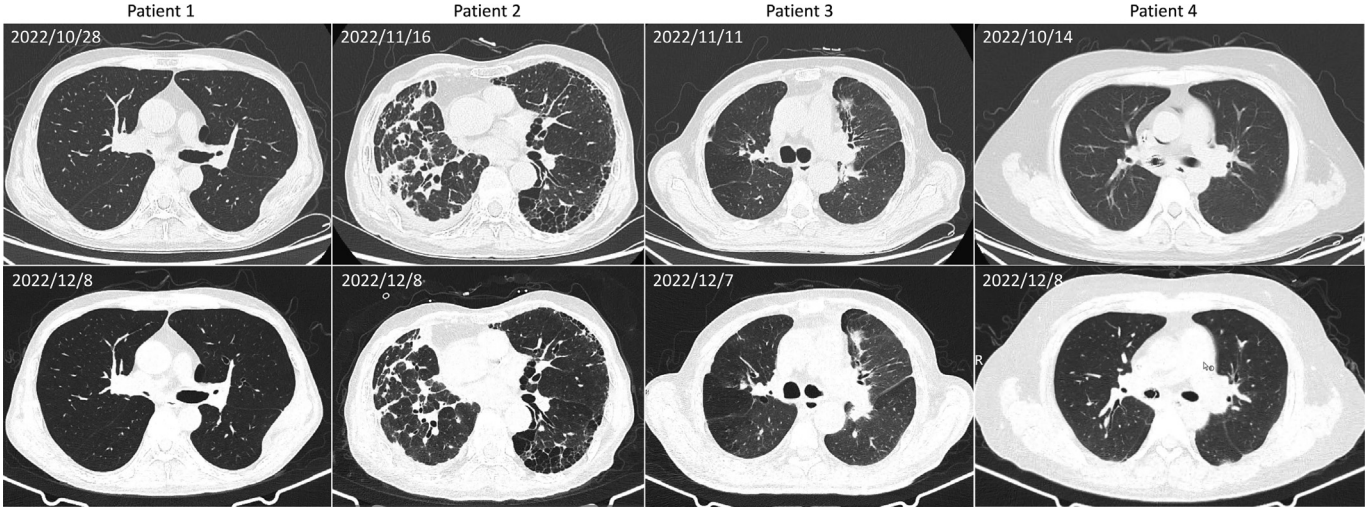

Fig. 2. Chest CT of the four LTx recipients before infected with SARS-CoV-2 (up panel). Chest CT obtained at 20 days, 20 days, 16 days, and 17 days after infected with SARS-CoV-2 of the four LTx recipients, respectively (down panel). Abbreviations: LT, lung transplant; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

tion of positive viral PCR testing was up to 25-28 days post-infection, although all of them received antiviral therapy.

3.3. Effects of NM/r on blood concentration of tacrolimus

All four recipients received tacrolimus at the time of SARS-CoV-2 infection (Table 1). During the first course of antiviral therapy, NM/r was started 12 h after the last dose of tacrolimus, and tacrolimus was maintained during the first 5-day course of antiviral therapy. Tacrolimus concentrations in Patient 3 were already supratherapeutic pre-NM/r treatment and persisted at high levels even two days after completing NM/r therapy. The patient presented with tremors, and rifampicin 0.3 g was given for two consecutive days to reduce tacrolimus levels, which decreased from 20.3 ng/mL to 12.4 ng/mL on day 1 and 2.6 ng/mL on day 2 after rifampicin. None of the other three cases had a supratherapeutic concentration at the first assessment after com-

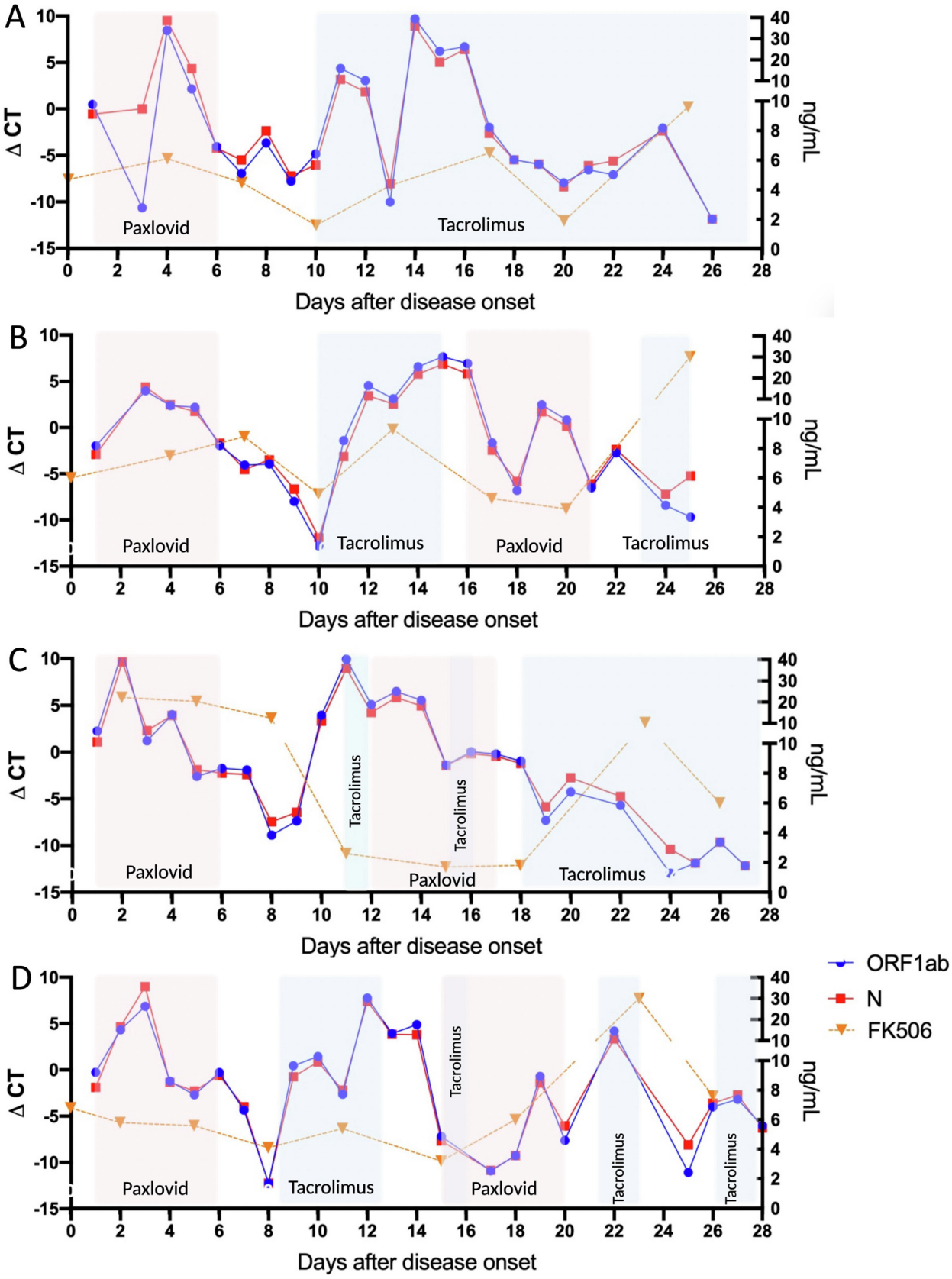

Fig. 3. Viral dynamic change in oropharyngeal samples and tacrolimus concentration of the four LTx recipients infected with SARS-CoV-2. Abbreviations: LT, lung transplant; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

pletion of NM/r. Tacrolimus was re-initiated at their baseline daily dose 3-4 days after NM/r therapy.

During the second 5-day course of antiviral therapy, Patients 3 and 4 were prescribed 0.5 mg tacrolimus on day 4 and 0.25 mg tacrolimus on day 1 of NM/r treatment, respectively. Regular tacrolimus was reinitiated 1 or 2 days after the second course of NM/r. All three recipients experienced a supratherapeutic tacrolimus concentration after resuming full pre-dose tacrolimus. Tacrolimus was withheld in Patients 2 and 4, and the dose was reduced in Patient 3.

4. Discussion

Compared with the general population, recipients of solid organ transplant have a higher risk of developing severe disease and have higher mortality rate after infection with SARS-Cov-2. A meta-analysis suggested that kidney transplant recipients hospitalized with COVID-19 had an average mortality rate of 23% [13]. Among all the solid organ transplant recipients, patients with LTx had the highest mortality rate after being infected with SARS-Cov-2, approximately 25% [14]. Up to 16% of LTx recipients infected with SARS-CoV-2/Omicron/B.1.1.529 developed severe or critical disease severity, although 76% of them received early antiviral therapy with stroma, remdesivir or molnupiravir [15].

Paxlovid (NM/r, 300/100 mg) was made clinically available by the U.S. Food and Drug Administration in December 2021 after Pfizer announced a dramatic result of a scheduled interim analysis of the study showing an 89% reduction in risk of hospitalization from COVID-19 compared to placebo. Real-world data suggest that with a 5-day course of this antiviral combination, NM/r could reduce the risk of severe COVID-19 or mortality in immunosuppressed patients in the era of Omicron[15]. However, the efficacy in LTx recipients is unclear. In this study, all four LTx cases received NM/r within two days of SARS-CoV-2 infection, and none progressed to severe COVID-19. It suggests that early use of NM/r in lung transplant patients may reduce the risk of developing severe disease. However, no concrete conclusion could be drawn due to the limitation of the small sample size, and more data are needed to investigate whether LTx recipients could benefit from NM/r therapy.

Significant concerns about the efficacy and safety of NM/r in LTx cases still exist[16]. “NM/r rebound,” described as the return of symptoms or rebound of viral levels, has recently been reported in the general population[17]. Another study revealed that 27% (3/11) of COVID-19 cases treated with a 5-day course of NM/r experienced a rebound in viral levels [18]. A retrospective study revealed that 2 of 14 kidney transplant recipients experienced SARS-CoV-2 viral rebound [19]. Immunosuppression management for LTx recipients has some unique features, usually starting with a combination of the calcineurin inhibitor, an anti-proliferative agent, corticosteroids, and an IL-2 blocker, followed by an individualized protocol [20]. However, the safety of NM/r and the virologic rebound in LTx have rarely been reported. In this study, we enrolled four LTx cases and monitored SARS-CoV-2 RNA regularly. Viral RNA copies in oropharyngeal swabs rebounded in all four recipients within 4 days after stopping the first round of a 5-days course NM/r treatment.

The causes of COVID-19 rebound after NM/r treatment remain unclear. Possible mechanisms mainly include drug resistance due to mutation, insufficient drug exposure, immune waning, and long-lived infected cells[21]. For now, the standard duration of NM/r treatment is 5 days, and it is not clear whether patients could benefit from additional treatment with NM/r. In this study, one of the LTx patients didn’t receive additional NM/r therapy after viral rebound. He still recovered gradually.

Another primary concern with NM/r is the harm of drug interactions due to the ritonavir component, which inhibits the CYP3A enzyme of the cytochrome P450 system and significantly increases the blood concentrations of CYP3A-dependent drugs, including cyclosporine, tacrolimus, and the mTOR inhibitors[22,23]. This study revealed that the blood concentration could be maintained at a baseline level by maintaining tacrolimus and starting NM/r 12 h after the last dose of tacrolimus in LTx [23]. Initiating tacrolimus at baseline dose after discontinuing NM/r for three days is relatively safe when the drug concentration approaches the therapeutic target. However, the effect of more prolonged treatment with NM/r on tacrolimus concentrations still needs to be further investigated. All three recipients who received a longer course of NM/r therapy experienced a supratherapeutic tacrolimus concentrations. Though all four patients did not present with acute kidney injury, hypertension, or liver dysfunction, more data are needed to explore the safety of a longer course NM/r to prevent a viral rebound and the optimal strategy for managing tacrolimus in conjunction with NM/r.

This study has several limitations. First, ΔCt values were used as a surrogate for viral load. Second, due to the limitation of the small sample size, we can only conclude that the 5-day course of NM/r was not enough and viral rebound was common. More data are needed to investigate whether LTx recipients could benefit from a longer course of NM/r therapy. Lastly, other medications that could potentially interact with NM/r were replaced with non-interacting drugs during antiviral therapy. For example, Atorvastatin was replaced with Pravastatin, and Enoxaparin replaced Rivaroxaban. The other potential drug interactions were not investigated in the study.

5. Conclusion

The 5-day course of NM/r treatment was insufficient for LTx recipients and viral load rebound was observed in all four recipients. More data are needed to clarify whether LTx's SARS-CoV-2 viral rebound could benefit from additional treatment with NM/r.

Ethics statement

This study was approved by the Ethics Committee of China-Japan Friendship Hospital (2022-KY-052). All information related to individuals in this study was pseudonymized.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Author contributions

Hui Li: Methodology, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Li Zhao:** Investigation, Formal analysis, Data curation, Writing – original draft. **Ke Huang:** Investigation, Formal analysis, Data curation, Writing – original draft. **Xiaoxing Wang:** Methodology, Investigation. **Fei Zhou:** Investigation, Formal analysis, Data curation, Writing – original draft. **Yiming Feng:** Investigation, Formal analysis, Data curation, Writing – original draft. **Liang Ma:** Methodology, Investigation. **Bin Cao:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition, Supervision, Resources. **Wenhui Chen:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition, Supervision, Resources.

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