Nirmatrelvir and ritonavir combination against COVID-19 caused by omicron BA.2.2: A single-center large observational study

Zhangzhang Chen[1], Can Chen[1], Ranyi Li[1], Shuliang Xing[2], Lei Cao[1], Yue Qu[3], Qianzhou Lv[1], and Xiaoyu Li[1]

[1]Zhongshan Hospital Fudan University
[2]Science and Education office Shanghai Geriatric Medical Center
[3]Alfred Hospital and Monash University

October 18, 2023

Abstract

Objective: To assess the effectiveness and safety of nirmatrelvir-ritonavir in the treatment of mild-to-moderate COVID-19 caused by the omicron BA. 2. 2 variant. **Methods:** An observational study was conducted retrospectively to review the outcomes of mild-to-moderate COVID-19 patients admitted between 26 April and 30 June, 2022. Patients' baseline characteristics were collected and assessed. Participants in the intervention group were administered nirmatrelvir-ritonavir in addition to standard care, whereas those in the control group only received standard care. The primary outcome was the duration between symptoms onset or the initial positive RT-PCR test and the subsequent conversion to a negative result. **Results:** The analysis included 324 patients who were administered nirmatrelvir-ritonavir and an equal number of control patients. The patient characteristics in both groups were evenly matched. The average duration from symptoms onset or the initial positive RT-PCR to negative conversion was similar in both groups (16.2±5.0 vs. 16.1±6.3 days, P=0.83). Control patients exhibited slower conversion in comparison to patients who received nirmatrelvir-ritonavir treatment within 10 days of symptom onset. **Conclusion:** These findings suggest that administering nirmatrelvir-ritonavir within 10 days of symptom onset could potentially reduce the time it takes for SARS-CoV-2-infected patients to negative RT-PCR results, thereby expanding the current usage guidelines for nirmatrelvir-ritonavir.

Nirmatrelvir and ritonavir combination against COVID-19 caused by omicron BA.2.2: A single-center large observational study

Can Chen[1#], Ranyi Li[1#], Shuliang Xing[2], Lei Cao[3], Yue Qu[4], Qianzhou Lv[1] , Xiaoyu Li[1*], Zhangzhang Chen[1*]

[1]Department of Pharmacy, Zhongshan Hospital, Fudan University, Shanghai, China

[2]Science and Education office, Shanghai Geriatric Medical Center, Shanghai, China

[3]Medical Administration Office, Zhongshan Hospital, Fudan University, Shanghai, China

[4]Department of Infectious Diseases, The Alfred Hospital and Monash University, Clayton, VIC 3000, Australia

[#] Can Chen and Ranyi Li contributed equally to this work and have shared first authorship.

*Corresponding authors:

Zhangzhang Chen, Department of Pharmacy, Zhongshan Hospital, Fudan University, 180# Fengling Road, 200032, Shanghai, China, Tel: +86-21-64041990-5062. Email: chen.zhangzhang@zs-hospital.sh.cn,

Xiaoyu Li, Department of Pharmacy, Zhongshan Hospital Fudan University, 180# Fengling Road, 200032, Shanghai, China, Tel: +86-21-64041990-5063. Email: Li.xiaoyu@zs-hospital.sh.cn

Key words: Nirmatrelvir-ritonavir, COVID-19, observational study

Abstract

Objective: To assess the effectiveness and safety of nirmatrelvir-ritonavir in the treatment of mild-to-moderate COVID-19 caused by the omicron BA. 2. 2 variant.

Methods: An observational study was conducted retrospectively to review the outcomes of mild-to-moderate COVID-19 patients admitted between 26 April and 30 June, 2022. Patients' baseline characteristics were collected and assessed. Participants in the intervention group were administered nirmatrelvir-ritonavir in addition to standard care, whereas those in the control group only received standard care. The primary outcome was the duration between symptoms onset or the initial positive RT-PCR test and the subsequent conversion to a negative result.

Results: The analysis included 324 patients who were administered nirmatrelvir-ritonavir and an equal number of control patients. The patient characteristics in both groups were evenly matched. The average duration from symptoms onset or the initial positive RT-PCR to negative conversion was similar in both groups (16.2±5.0 vs. 16.1±6.3 days, P=0.83). Control patients exhibited slower conversion in comparison to patients who received nirmatrelvir-ritonavir treatment within 10 days of symptom onset.

Conclusion: These findings suggest that administering nirmatrelvir-ritonavir within 10 days of symptom onset could potentially reduce the time it takes for SARS-CoV-2-infected patients to negative RT-PCR results, thereby expanding the current usage guidelines for nirmatrelvir-ritonavir.

Keywords : Nirmatrelvir-ritonavir, COVID-19, observational study

Introduction

The rapid development of therapeutics and preventive strategies for COVID-19 has occurred during the worldwide pandemic[1,2]. While vaccines can effectively prevent severe illness caused by COVID-19, the immune response they trigger may diminish over time and become less effective against emerging variants. This highlights the importance of antiviral therapies for SARS-CoV-2 infection.

Comprising two antiviral protease inhibitors, nirmatrelvir-ritonavir stands out as a highly potent medication for combating SARS-CoV-2. Nirmatrelvir, an oral antiviral medication, hinders the replication of viruses by focusing on the primary protease (Mpro) of SARS-CoV-2[3]. Nirmatrelvir exhibits comparable effectiveness against both the original SARS-CoV-2 strain and its subsequent variants due to the highly preserved sequence of Mpro in coronaviruses. The plasma concentrations of nirmatrelvir are elevated due to ritonavir's inhibition of CYP3A-mediated metabolism. Therefore, combining nirmatrelvir and ritonavir may maximize the therapeutic benefit[3, 9]. In the recent EPIC-HR study published by Hammond et al. (2022), patients with mild to moderate COVID-19 who were susceptible to developing severe illness within 5 days of experiencing symptoms were administered nirmatrelvir-ritonavir. As a result, they demonstrated a reduced likelihood of hospitalization or succumbing to the disease. Following this randomized trial[10], numerous countries have granted emergency use authorization to nirmatrelvir-ritonavir for the management of COVID-19.

Medical service providers in China are responsible for monitoring or treating high-risk COVID-19 patients. From March, 2022[11], nirmatrelvir-ritonavir has been one of the few treatment choices that were accessible for prescription locally. In the EPIC-HR study[10], the examined groups were comparatively youthful, with obesity being the most frequently cited risk factor for progressing to severe illness. In China and many other countries such as Australia, the majority of COVID-19 patients at high risk are elderly individuals who have various underlying comorbidities including hypertension, diabetes, and cardiovascular diseases. The purpose of this study was to evaluate the effectiveness of nirmatrelvir-ritonavir in the elderly population in real-world scenarios, and provide guidance for clinical and policy decision-making.

Methods

Patients, setting and human ethical approvals

This retrospective observational study, conducted at the Shanghai Geriatric Medical Center (Meilong Branch of Zhongshan Hospital, Fudan University), examined individuals with COVID-19 who were hospitalized from 26th April to 30th June 2022. The Shanghai Geriatric Medical Center is a specialized medical facility that admits patients with COVID-19 in Shanghai for treatment. The omicron sublineage BA.2.2 was the primary cause of COVID-19 cases reported in Shanghai during this time frame[16].

Patients admitted for SARS-CoV-2 burden rebound were excluded if they had one RT-PCR test during their hospitalization and the result is negative, a severe COVID-19 diagnosis upon hospitalization, or insufficient information in the electronic medical record. The patient's infection severity was categorized based on the Diagnosis and Treatment Guideline for COVID-19 (Trial Version 9) issued by the China National Health Commission[12]. Mild COVID-19 refer to individuals experiencing one or multiple mild symptoms such as pyrexia, tussis, pharyngitis, asthenia, myalgia, anosmia and no concomitant pneumonia. Patients with moderate COVID-19 exhibit symptoms similar to those with mild disease, but they also show radiologic signs of pneumonia. The high-risk group for severe COVID-19 includes individuals aged 60 years or older who have a medical history of hypertension, cardiovascular diseases, cerebral infarction, chronic liver or kidney diseases, cancers, smoking, or obesity[13-15]. This analysis only included individuals who were diagnosed with mild or moderate cases of COVID-19 and were deemed to be at a high risk of developing severe illnesses. Patients were excluded if they had contraindications to nirmatrelvir-ritonavir, severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min per 1.73 m^2, undergoing dialysis, or had undergone renal transplantation), or severe liver impairment (cirrhosis, hepatocellular carcinoma, or had undergone liver transplantation).

This study adhered to STROBE guidelines and received approval from the ethics committees of Zhongshan Hospital, Fudan University (approval number B2022-470R). Due to the exceptional circumstances of the COVID-19 outbreak, this retrospective study utilizing de-identified information did not necessitate individual patient-informed consent.

Baseline characteristics of the patients

Upon hospital admission, patients' baseline characteristics were gathered, including sex, age, clinical classification(i.e., severity of symptoms), underlying health conditions, risk factors of developing severe illness, and immunization record. The number of days from the onset of symptoms or a positive RT-PCR test to hospitalization and to initiation of treatment were calculated. Within 2 days of being admitted to the hospital, respiratory samples were obtained from the upper respiratory tract of patients using a nasopharyngeal swab. The samples underwent testing using a real-time fluorescence quantitative RT-PCR method to detect the presence of the SARS-CoV-2 virus. The targets for the RT-PCR assay were open reading frame 1ab (ORF), nucleocapsid protein gene (N gene) and envelope protein gene (E gene). All the targets were recorded with the cycle threshold (Ct) value, which represents the number of cycles required to amplify the viral nucleic acid to a detectable level. A Ct value below 35 for ORF, N gene or E gene was used to define a positive sample of SARS-CoV-2[17].

Intervention and control

Every patient was provided with standard care, which involved resting in bed, monitoring vital signs, measuring oxygen saturation, conducting routine blood chemistry and urine analysis, examining biochemical indicators such as liver and myocardial enzymes and renal function, assessing coagulation parameters, analyzing arterial blood gas, conducting chest imaging and cytokine detection, and administering oxygen therapy if necessary. Individuals in the intervention cohort were administered nirmatrelvir at a dosage of 300 mg alongside ritonavir at a dosage of 100 mg, twice a day, for a duration of 5 days. Alternatively, if patients' eGFR ranged from 30-59 mL/min per 1.73 m^2, the dosage of nirmatrelvir was reduced to 150 mg while ritonavir remained at 100 mg. Patients in the control group only obtained standard care and were not ad-

ministered nirmatrelvir-ritonavir. Patients in both groups did not receive any other medications specifically for COVID-19, such as remdesivir or monoclonal antibodies.

Primary outcome

The primary outcome was the duration until conversion, which is defined as the time between the appearance of symptoms or the initial positive RT-PCR test and the second negative RT-PCR test outcome. From the second day of hospitalization onwards, all patients underwent daily RT-PCR testing using nasopharyngeal swabs until two consecutive negative results were obtained. According to China's COVID-19 diagnosis and treatment guideline Trial Version 9, criteria for ending isolation and discharge involve obtaining two consecutive tests result with Ct values of [?]35 for ORF, N, and E genes with an interval of more than 24 hours[12, 18].

Secondary outcomes and safety assessment

Secondary outcomes included the proportion of individuals with a negative RT-PCR test for respiratory SARS-CoV-2 on the 15^{th} day after the onset of symptoms or on the 15^{th} day after the initial positive RT-PCR test, incidence of turning critically ill, needs for mechanical ventilation and oxygen therapy. In addition, a safety evaluation of the nirmatrelvir-ritonavir was conducted by examining the medical records of patients to identify potential adverse effects (AEs) such as diarrhea and stomach discomfort. Monitoring for AEs began at the start of treatment and continued until the patient was released from the hospital.

Statistical analyses

Propensity score matching was employed based on age, sex, COVID-19 type upon admission, commodities (including diabetes mellitus, malignancy, stroke, hypertension, cardiovascular diseases, pulmonary diseases), vaccination status, and medications administered during hospitalization such as corticosteroids (prednisone, dexamethasone, hydrocortisone, methylprednisolone), antibiotics (β-lactams, moxifloxacin, levofloxacin, metronidazole, vancomycin, azithromycin, linezolid, tigecycline, caspofungin, voriconazole), antiviral drugs (entecavir, valacyclovir), Chinese traditional medications (Lianhua Qingwen Granules, Qingkailing Soft Capsules, Jinhua Qinggan Granules, Shufeng Jiedu Capsules), immunomodulator (recombinant human interferon α2b injection, human interleukin-11 for injection, human Granulocyte colony stimulating factor injection, intravenous human immunoglobulin, thymalfasin), and Chinese decoctions in a logistic regression model. The propensity-score matching without replacement, utilizing a caliper width of 0.2. The standardized mean differences (SMDs) for each covariate between the groups prior to and following the propensity-score matching were calculated. These differences were considered balanced if the SMD was less than the threshold of 0.1. The evaluation of results was conducted using Kaplan-Meier curves. Furthermore, the study also performed subgroup analysis on the time to conversion from RT-PCR positive to negative status for SARS-CoV-2. The specific subgroup analyses considered factors such as patients' age ([?]60 years versus >60 years), clinical classification, and vaccination history (fully vaccinated versus partially vaccinated). Additionally, the subgroup analysis was stratified based on the time interval between the administration of nirmatrelvir-ritonavir and the onset of symptoms or the first positive RT-PCR test. All the analyses were performed using software SPSS 26.0 and R 4.2.1. Statistical tests were 2-side and the statistical significance level set at $P < 0.05$.

RESULTS

Demographic characteristics of the patients

During the designated study period, Shanghai Geriatric Medical Centre admitted a total of 5524 patients who were diagnosed with SARS-CoV-2 infections. After removing subjects that did not meet inclusion criteria, the study included 3025 patients. Nirmatrelvir-ritonavir was given to 324 patients [5.8%]. The control group consisted of carefully selected 324 patients from the retrospective cohort, with baseline characteristics used as matching criteria (Figure 1). Following the matching process, patient characteristics were comparable between the nirmatrelvir-ritonavir and control cohorts at baseline, with all SMDs below 0.1, except for the

duration from the initial positive PCR test to hospitalization (SMD=-0.43), RT-PCR Ct value upon admission (SMD=-0.59), administration of corticosteroids (SMD=0.11) and administration of antiviral medication (SMD=0.10). The baseline characteristics of patients treated with or without nirmatrelvir-ritonavir are displayed in Table 1. Overall, less than one-third of the group were completely immunized, with 194 individuals (29.9%) having been administered at least one dose of the SARS-CoV-2 vaccine. Most of the patients were over the age of 65, and the median age was 77 years old (interquartile range [IQR], 67-88 years). 314 (48.4%) patients were men. 547 (84.4%) were classified as mild cases. The prevalent underlying conditions consisted of individuals aged [?]65 years (530 [81.8%]), hypertension (311 [48.0%]), and diabetes (144 [22.2%]); more than one risk factor was present in 432 (66.7%) patients. There was no significant difference found between the nirmatrelvir-ritonavir and matched control groups.

Application of nirmatrelvir-ritonavir for primary and secondary outcomes

The mean time from symptom onset or the first positive RT-PCR result to negative RT-PCR results was similar in both the treatment and control groups (16.2±5.0 vs. 16.1±6.3 days, P = 0.83, Table 2). Figure 2 displays the Kaplan-Meier survival curve for the primary outcome. No correlation was observed between the time to conversion of RT-PCR results and patients' age, clinical classification, concurrent medication usage, or prior vaccination in the analysis of individuals treated with nirmatrelvir-ritonavir, except in the case of the usage of antibiotics (Figure 4). Following the appearance of symptoms or the initial RT-PCR confirmation, 92% of nirmatrelvir-ritonavir was administered within 14 days, while 82% and 64% were taken within 10 and 7 days respectively (Figure 3). Hence, the subgroup analysis was further stratified based on the time interval between the administration of nirmatrelvir-ritonavir and the onset of symptoms or the first positive RT-PCR test. Patients who received nirmatrelvir-ritonavir within 10 days of experiencing symptoms demonstrated quicker conversion of RT-PCR results compared to the control group that was matched (Figure 5).

No significant difference was found between the two groups in the percentage of patients who tested negative for respiratory SARS-CoV-2 using RT-PCR 15 days after the onset of symptoms (47.2% vs 50.0%, P=0.53). Additionally, the two groups did not differ significantly with respect to the progression to more severe conditions, such as turning to critically ill (1.9% vs 1.9%, P = 1), need for mechanical ventilation (0.3% vs 1.5%, P = 0.21), and the need for oxygen therapy (2.5% vs 3.4%, P = 0.64).

Evaluation of the safety of nirmatrelvir-ritonavir in COVID patients at high risk

Among patients treated with nirmatrelvir-ritonavir, 64 patients reported the adverse effects. Out of these patients, 19 (29.7%) encountered at least one form of adverse effects, with gastrointestinal disorders (21.8%) being the prevailing side effects (Table 3).

Discussion

In May 2023, the global health emergency of COVID-19 was officially terminated by the World Health Organization. The attention for COVID-19 care and treatment has now been redirected towards the vulnerable population who are at a higher risk of developing more serious COVID-19-associated illnesses. In the midst of a widespread Omicron outbreak and high vaccination rates, our study revealed that the utilization of nirmatrelvir-ritonavir did not result in a more rapid elimination of respiratory SARS-CoV-2 in patients at high risk.

Interestingly, the examination centered on individuals who received nirmatrelvir-ritonavir treatment within 10 days after symptoms onset or first positive RT-PCR test. It revealed a faster conversion from positive to negative RT-PCR tests when compared to untreated patients. The study also found that the shorter the time between the onset of symptoms or the first positive RT-PCR test and the administration of nirmatrelvir-ritonavir, the faster the conversion to RT-PCR negativity. This indicates that the timing of nirmatrelvir-ritonavir therapy initiation following the onset of symptoms is a crucial indicator in achieving rapid elimination of the virus. Our findings align with a recent study[19] which indicated that the administration of nirmatrelvir-ritonavir may accelerating the conversion of negative RT-PCR respiratory SARS-CoV-2. Additionally, our study expands upon the findings of the EPIC-HR study[10], which included unvaccinated

and non-hospitalized adults from various racial backgrounds. In contrast, our study specifically examined Asian adult patients at high risk who were hospitalized, fully or partially vaccinated and generally "older".

RT-PCR testing has been utilized to detect SARS-CoV-2 in the upper respiratory tract[20]. The Ct values of RT-PCR represent the number of amplification cycles needed for the target gene to exceed a threshold level, potentially offering semi-quantitative or indirect measurements of viral load[21]. Previous studies have analyzed the temporal trends in Ct values over the course of a SARS-CoV-2 infection. The lowest Ct values (indicating a higher concentration of viral RNA) are observed shortly after the onset of symptoms and are significantly correlated with the time elapsed since onset. Higher Ct values may be linked to better outcomes in COVID-19 individuals, decreased possibility of progression to severe illness, decreased disease severity, decreased mortality, and absence of biochemical and haematological markers[21]. The RT-PCR Ct value was frequently used as an alternative measure of viral load, serving as a measure of infectivieness. According to this research, the administration of nirmatrelvir-ritonavir within 10 days of the symptom onset resulted in a quicker rise in RT-PCR Ct value, thus reducing the duration of isolation. It is reported that early administration of nirmatrelvir-ritonavir in patients could lead to a quicker cessation of virus shedding, thereby reducing the risk of disease transmission and expediting recovery from COVID-19[21].

Previous study noted that SARS-CoV-2 viral replication at multiple sites outside the respiratory tract during the first two weeks after the onset of symptoms[22]. The peak viral load of SARS-CoV-2 typically occured around the time of symptoms onset, followed by a gradual decline[23]. In severely ill patients, viral replication can continue for several months[22]. Based on the findings mentioned above, it should be considered that patients with COVID-19 more than 5 days post-onset and/or severe illness are highly probable to derive benefits from nirmatrelvir-ritonavir therapy. This is due to the continued presence of the virus in the body, particularly in the respiratory system, among patients in the early (within 14 days after symptoms onset), intermediate (15-30 days), and late (31 days or longer) COVID-19 patients. At this time, nirmatrelvir-ritonavir is given to clear the virus, which theoretically benefits the patient's recovery and may even prevent their death. Furthermore, owing to the scarcity of COVID-19 healthcare facilities in Shanghai during the initial six months of 2022, a number of individuals testing positive for PCR were unable to receive immediate admission following infection, resulting in a disease duration exceeding 5 days upon admission. Therefore, many patients admitted in Shanghai Geriatric Medical Center did not receive nirmatrelvir-ritonavir until RT-PCR was positive or symptoms occurred more than 5 days. The current research validated that administering nirmatrelvir-ritonavir within 5 to 10 days of symptom onset or a positive RT-PCR test could expedite the conversion to a negative result.

The limitation of the current study cannot be ignored. The study is a single-centered retrospective observational study with potential residual confounding and selection bias. Because the study was conducted retrospectively, a detailed analysis of adverse events and rebound were not performed, as the data in medical records regarding these topics were sometime inconsistent.

Conclusion

To summarize, the use of nirmatrelvir-ritonavir within 10 days of symptom onset or a positive RT-PCR result is linked to a reduced duration of RT-PCR conversion in high-risk patients infected with SARS-CoV-2. This expands the potential use of nirmatrelvir-ritonavir beyond its labeled indications.

Conflict of interest

None.

Funding

The research was funded by the Shanghai Key Clinical Specialty Construction Project (grant number shslczdzk06504).

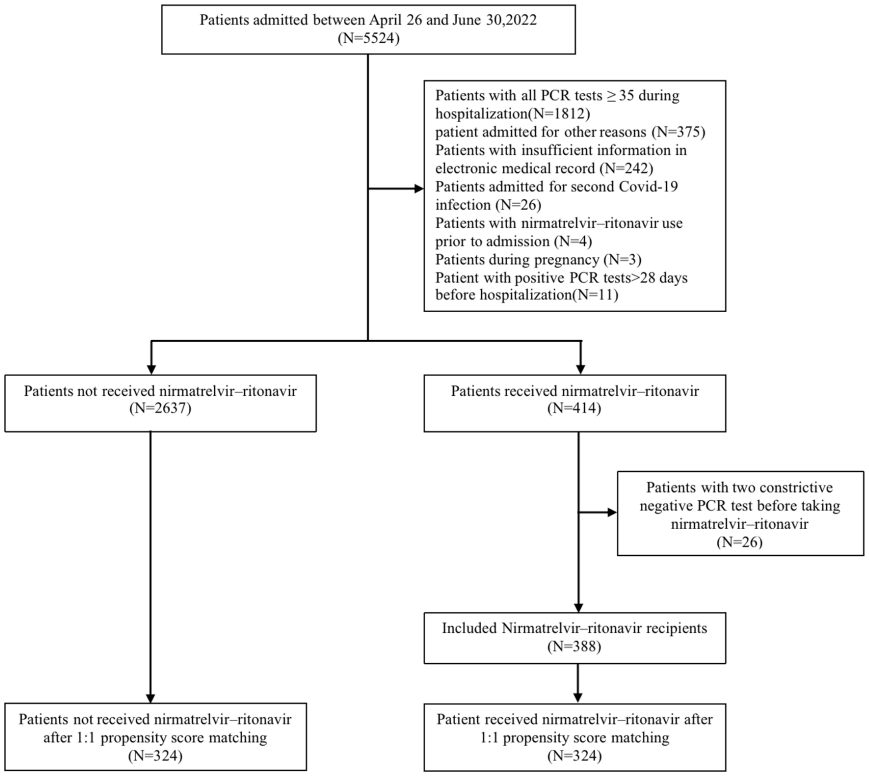
Author Contributions

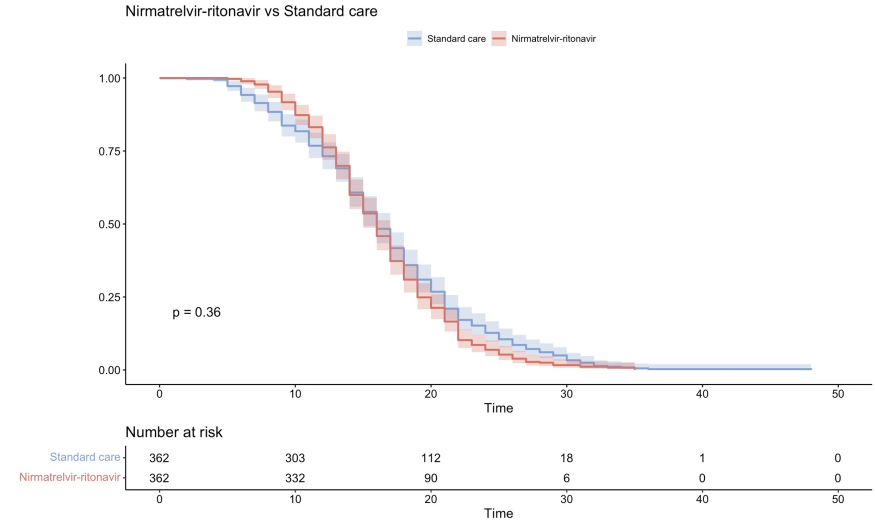
ZZ.C, XY.L, and QZ.L initiated the study and acquired the data. The data was processed and analyzed by RY.L and C.C, who also wrote the manuscript. SL.X, L.C, and Y.Q revised the manuscript. All authors approved the final version of the work.

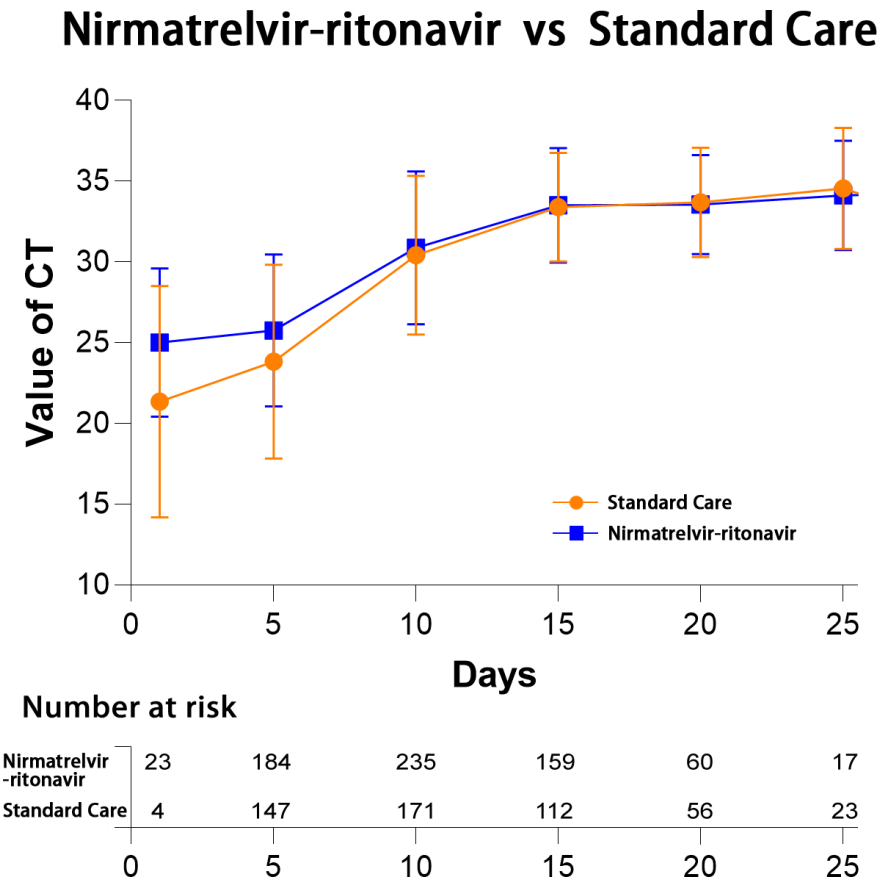
Reference

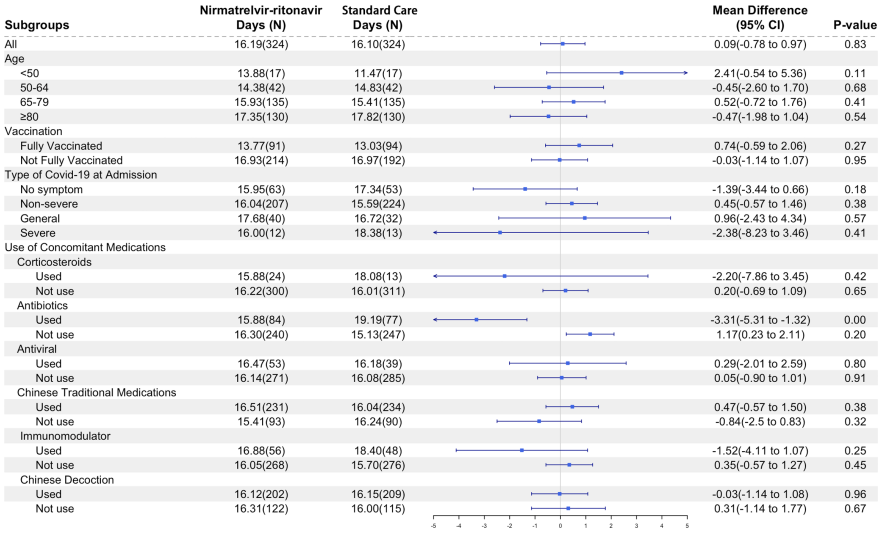
1. Pan H, Peto R, Henao-Restrepo AM, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med, 2021, 384(6):497-511.
2. Krammer F. SARS-CoV-2 vaccines in development. Nature, 2020, 586(7830):516-27.
3. Owen DR, Allerton CMN, Anderson AS, et al. An oral SARS-CoV-2 Mpro inhibitor clinical candidate for the treatment of COVID-19. Science, 2021, 374(6575):1586-93.
4. Anand K, Ziebuhr J, Wadhwani P, et al. Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs. Science, 2003, 300(5626):1763-7.
5. Vangeel L, Chiu W, De Jonghe S, et al. Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. Antiviral Res, 2022, 198(105252.
6. Ullrich S, Ekanayake KB, Otting G, et al. Main protease mutants of SARS-CoV-2 variants remain susceptible to nirmatrelvir. Bioorg Med Chem Lett, 2022, 62(128629.
7. Singh RSP, Toussi SS, Hackman F, et al. Innovative Randomized Phase I Study and Dosing Regimen Selection to Accelerate and Inform Pivotal COVID-19 Trial of Nirmatrelvir. Clin Pharmacol Ther, 2022, 112(1):101-11.
8. Dal-Ré R, Becker SL, Bottieau E, et al. Availability of oral antivirals against SARS-CoV-2 infection and the requirement for an ethical prescribing approach. Lancet Infect Dis, 2022, 22(8):e231-e8.
9. Sevrioukova IF, Poulos T L. Structure and mechanism of the complex between cytochrome P4503A4 and ritonavir. Proc Natl Acad Sci U S A, 2010, 107(43):18422-7.
10. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med, 2022, 386(15):1397-408.
11. National Medical Products Administration of China. Emergency conditional approval of Pfizer's COVID-19 therapy:nirmatrelvir tablet/ritonavir tablet combination package (i.e. Paxlovid) importation registration [in Chinese]. Available at: https://www. nmpa. gov. cn/yaowen/ypjgyw/20220212085753142. html. Accessed 27 April 2022.
12. National Health Commission of the People's Republic of China. Diagnosis and treatment protocol for COVID-19 (trial version 9) [in Chinese]. Available at: http://www. nhc. gov. cn/cms-search/xxgk/getManuscriptXxgk. htm?id=b74ade1b a4494583805a3d2e40093d88. Accessed 20 June 2022.
13. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369:m1985.
14. Kim L, Garg S, O'Halloran A, et al. Risk Factors for Intensive Care Unit Admission and In-hospital Mortality Among Hospitalized Adults Identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). Clin Infect Dis, 2021, 72(9):e206-e14.
15. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China:Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA, 2020, 323(13):1239-42.
16. Zhang X, Zhang W, Chen S. Shanghai's life-saving efforts against the current omicron wave of the COVID-19 pandemic. Lancet, 2022, 399(10340):2011-2.
17. Drew RJ, O'Donnell S, LeBlanc D, et al. The importance of cycle threshold values in interpreting molecular tests for SARS-CoV-2. Diagn Microbiol Infect Dis, 2020, 98(3):115130.
18. Zhang R, Liang H, Tang J. Negative Conversion Rate of SARS-CoV-2 Infection. JAMA Intern Med, 2021, 181(4):566.
19. Li H, Gao M, You H, et al. Association of Nirmatrelvir/Ritonavir Treatment on Upper Respiratory Severe Acute Respiratory Syndrome Coronavirus 2 Reverse Transcription-Polymerase Chain Reac-

tion (SARS-Cov-2 RT-PCR) Negative Conversion Rates Among High-Risk Patients With Coronavirus Disease 2019 (COVID-19). Clin Infect Dis, 2023, 76(3):e148-e54.
20. Salvatore PP, Dawson P, Wadhwa A, et al. Epidemiological Correlates of Polymerase Chain Reaction Cycle Threshold Values in the Detection of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis, 2021, 72(11):e761-e7.
21. Rao SN, Manissero D, Steele VR, et al. A Systematic Review of the Clinical Utility of Cycle Threshold Values in the Context of COVID-19. Infect Dis Ther, 2020, 9(3):573-86.
22. Stein SR, Ramelli SC, Grazioli A, et al. SARS-CoV-2 infection and persistence in the human body and brain at autopsy. Nature, 2022, 612(7941):758-63.
23. Rodriguez-Grande C, Adan-Jimenez J, Catalan P, et al. Inference of Active Viral Replication in Cases with Sustained Positive Reverse Transcription-PCR Results for SARS-CoV-2. J Clin Microbiol. 2021;59(2):e02277-20.**Figure legends**Figure 1 The flow chart of the process used to screen eligible patients. Figure 2 Kaplan-Meier curve of primary outcome for nirmatrelvir-ritonavir recipients versus matched control group Figure 3 Change of RT-PCR Ct value for nirmatrelvir-ritonavir recipients versus matched control group Figure 4 Subgroup analysis of the mean difference of time to PCR negative for nirmatrelvir-ritonavir recipients versus matched control group Figure 5 Subgroup analysis of the mean difference of time to viral clearance for patients with different nirmatrelvir-ritonavir initiation time versus matched control group

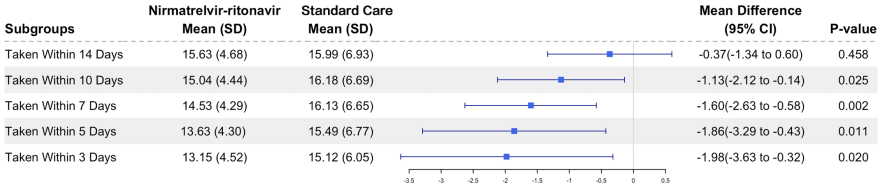








Subgroups	Nirmatrelvir-ritonavir Days (N)	Standard Care Days (N)	Mean Difference (95% CI)	P-value
All	16.19(324)	16.10(324)	0.09(-0.78 to 0.97)	0.83
Age				
<50	13.88(17)	11.47(17)	2.41(-0.54 to 5.36)	0.11
50-64	14.38(42)	14.83(42)	-0.45(-2.60 to 1.70)	0.68
65-79	15.93(135)	15.41(135)	0.52(-0.72 to 1.76)	0.41
≥80	17.35(130)	17.82(130)	-0.47(-1.98 to 1.04)	0.54
Vaccination				
Fully Vaccinated	13.77(91)	13.03(94)	0.74(-0.59 to 2.06)	0.27
Not Fully Vaccinated	16.93(214)	16.97(192)	-0.03(-1.14 to 1.07)	0.95
Type of Covid-19 at Admission				
No symptom	15.95(63)	17.34(53)	-1.39(-3.44 to 0.66)	0.18
Non-severe	16.04(207)	15.59(224)	0.45(-0.57 to 1.46)	0.38
General	17.68(40)	16.72(32)	0.96(-2.43 to 4.34)	0.57
Severe	16.00(12)	18.38(13)	-2.38(-8.23 to 3.46)	0.41
Use of Concomitant Medications				
Corticosteroids				
Used	15.88(24)	18.08(13)	-2.20(-7.86 to 3.45)	0.42
Not use	16.22(300)	16.01(311)	0.20(-0.69 to 1.09)	0.65
Antibiotics				
Used	15.88(84)	19.19(77)	-3.31(-5.31 to -1.32)	0.00
Not use	16.30(240)	15.13(247)	1.17(0.23 to 2.11)	0.20
Antiviral				
Used	16.47(53)	16.18(39)	0.29(-2.01 to 2.59)	0.80
Not use	16.14(271)	16.08(285)	0.05(-0.90 to 1.01)	0.91
Chinese Traditional Medications				
Used	16.51(231)	16.04(234)	0.47(-0.57 to 1.50)	0.38
Not use	15.41(93)	16.24(90)	-0.84(-2.5 to 0.83)	0.32
Immunomodulator				
Used	16.88(56)	18.40(48)	-1.52(-4.11 to 1.07)	0.25
Not use	16.05(268)	15.70(276)	0.35(-0.57 to 1.27)	0.45
Chinese Decoction				
Used	16.12(202)	16.15(209)	-0.03(-1.14 to 1.08)	0.96
Not use	16.31(122)	16.00(115)	0.31(-1.14 to 1.77)	0.67



Subgroups	Nirmatrelvir-ritonavir Mean (SD)	Standard Care Mean (SD)	Mean Difference (95% CI)	P-value
Taken Within 14 Days	15.63 (4.68)	15.99 (6.93)	-0.37(-1.34 to 0.60)	0.458
Taken Within 10 Days	15.04 (4.44)	16.18 (6.69)	-1.13(-2.12 to -0.14)	0.025
Taken Within 7 Days	14.53 (4.29)	16.13 (6.65)	-1.60(-2.63 to -0.58)	0.002
Taken Within 5 Days	13.63 (4.30)	15.49 (6.77)	-1.86(-3.29 to -0.43)	0.011
Taken Within 3 Days	13.15 (4.52)	15.12 (6.05)	-1.98(-3.63 to -0.32)	0.020

Hosted file

Table 1.docx available at https://authorea.com/users/311780/articles/672856-nirmatrelvir-and-ritonavir-combination-against-covid-19-caused-by-omicron-ba-2-2-a-single-center-large-observational-study

Hosted file

Table 2.docx available at https://authorea.com/users/311780/articles/672856-nirmatrelvir-and-ritonavir-combination-against-covid-19-caused-by-omicron-ba-2-2-a-single-center-large-observational-study

Hosted file

Table 3.docx available at https://authorea.com/users/311780/articles/672856-nirmatrelvir-and-ritonavir-combination-against-covid-19-caused-by-omicron-ba-2-2-a-single-center-large-observational-study