Infection and Drug Resistance

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ORIGINAL RESEARCH

A Real-World Retrospective Study on the Efficacy and Safety of Four Antiviral Drugs for Hospitalized COVID-19 Patients: Nirmatrelvir/Ritonavir, Simnotrelvir/Ritonavir, Molnupiravir and Azvudine

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Purpose: This retrospective study aims to compare the effectiveness and safety of four oral antiviral drugs including Simnotrelvir/Ritonavir, Nirmatrelvir/Ritonavir, Azvudine and Molnupiravir in hospitalized patients with Coronavirus Disease 2019 (COVID-19) in a real-world setting, providing evidence to guide clinical practice against COVID-19.

Patients and Methods: Patients with mild or moderate COVID-19 hospitalized at Wuxi City's Second People's Hospital during December 2022 to June 2023 were included in this study. Patients were grouped by the antiviral drug received. The primary endpoint was the length of hospital stay. Patients were further divided into subgroups for stratified analysis, considering age, timing of medication, and drug mechanisms, to explore whether these factors could influence the treatment efficacy.

Results: Of the enrolled 195 patients receiving any treatment, 42 received Nirmatrelvir/Ritonavir, 33 received Molnupiravir, 81 received Simnotrelvir/Ritonavir, and 39 received Azvudine. Patients in Nirmatrelvir/Ritonavir and Simnotrelvir/Ritonavir groups had significantly shorter hospital stays compared to those in Azvudine group ($P < 0.05$). No significant difference was observed in hospital stays between those initiating antiviral therapy within or more than five days after symptom onset ($P = 0.1109$). Among patients with comorbidities, the Nirmatrelvir/Ritonavir and Simnotrelvir/Ritonavir group showed shorter hospital stays than the Azvudine group ($P < 0.05$). No serious treatment-related adverse events were observed across the groups.

Conclusion: In this retrospective study, Nirmatrelvir/Ritonavir and Simnotrelvir/Ritonavir exerts stronger potency on reducing duration of hospital stays in hospitalized patient with COVID-19, suggestive of a better choice for antiviral therapy. Patients who fail to take antiviral drugs in time after symptom onset would still benefit from these antiviral regimens. Additional well-designed clinical trials with large sample size are still needed to further confirm the effectiveness of these antivirals.

Keywords: antivirals, COVID-19, molnupiravir, simnotrelvir/ritonavir, azvudine, nirmatrelvir/ritonavir

Introduction

Since 2019, the novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2), and its variants have caused a global pandemic. According to the World Health Organization (WHO), as of 21 July 2024, over

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775 million confirmed cases and more than seven million deaths have been reported globally since the beginning of pandemic.[1] Faced with this enormous challenge, WHO recommends antiviral therapies for hospitalized COVID-19 patients to reduce mortality.[2,3] Antiviral drugs, including Simnotrelvir/Ritonavir, Nirmatrelvir/Ritonavir, Azvudine, and Molnupiravir, which have been clinically validated, are included in the latest COVID-19 diagnosis and treatment guidelines in China.[4]

Molnupiravir is an RNA-dependent RNA polymerase (RdRp) inhibitor. As a substrate of RdRp, it participates in viral RNA synthesis by forming stable base pairs with G or A in the RdRp active site, leading to errors in viral RNA replication and ultimately blocking the replication of the SARS-CoV-2 virus.[5] Azvudine is also a broad-spectrum RNA virus inhibitor that can inhibit RdRp of the SARS-CoV-2 virus. During the synthesis process, it is incorporated into the viral RNA, blocking RNA extension, terminating RNA chain synthesis, and ultimately halting viral replication.[6–8] Nirmatrelvir is a 3-chymotrypsin-like protease (3CLpro) inhibitors that inhibits the viral protease 3CLpro, which is essential for viral replication. By preventing the cleavage of viral polyproteins, it effectively stops viral replication. Cytochrome P450 3A (CYP3A) is one of the most important cytochrome P450 isoforms responsible for drug metabolism by humans, and its encoding gene is CYP3A. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby increasing its plasma concentration.[9] Simnotrelvir/Ritonavir, the first China-developed targeted 3CLpro inhibitor, acts on the same target as Nirmatrelvir in Nirmatrelvir/Ritonavir.[10,11]

Real-world studies based on hospital patient data can better reflect real-life situations, thus providing significant assistance in evaluating drug efficacy and selecting clinical treatment regimens.A real-world study with hospitalization and death as endpoints demonstrated that participants receiving three antiviral drugs, Molnupiravir, Nirmatrelvir/Ritonavir, and Simnotrelvir/Ritonavir, had a 35% lower adjusted hazard ratio (95% CI: 18–49%) compared to untreated participants.[12] Studies comparing Nirmatrelvir/Ritonavir and Azvudine have shown Azvudine had potential clinical benefits in diabetic patients, chronic kidney disease patients, and moderate patients upon admission.[13] An emulation of a randomized target trial which assesses the effectiveness of azvudine and Nirmatrelvir/Ritonavir found that azvudine reduced all-cause death (Hazard ratio [HR]: 0.31; 95% CI: 0.12–0.78), Nirmatrelvir/ritonavir reduced invasive mechanical ventilation (HR: 0.42; 95% CI: 0.17–1.05), and its composite with all-cause death (HR: 0.38; 95% CI: 0.18–0.81).[14] Another real-world study showed no substantial differences in the risk of severe COVID-19 outcomes between patients treated with Nirmatrelvir/Ritonavir and Molnupiravir.[15] Nevertheless, there have been no head-to-head real-world studies conducted on these four drugs to date.

The Second People's Hospital of Wuxi treated hospitalized patients diagnosed with COVID-19 using four different oral antiviral drugs from December 1, 2022, to June 30, 2023. This study conducted a unique head-to-head comparison of Simnotrelvir/Ritonavir, Nirmatrelvir/Ritonavir, Molnupiravir, and Azvudine, providing the first comprehensive evaluation of their effectiveness and safety within a single cohort. Medical records of patients who received any of these drugs were analyzed, focusing on the length of hospital stay as the primary outcome. We conducted extensive subgroup analyses based on drug mechanisms, the timing of medication, and patient age, which provided nuanced insights into the optimal selection and timing of antiviral treatments for diverse patient demographics.

During the study period, nationwide genomic sequence analysis of indigenous cases of the novel coronavirus showed that all cases were of the Omicron variant, with the predominant strains being BA.5.2 and its sublineage (accounting for 66.2%) and BF.7 and its sublineage (accounting for 29.8%).Jiangsu Province was dominated by the BA.5.2 strain and its sublineage.[16]

Materials and Methods

Study Design and Patients

This retrospective study was based on real-world data collected from the Second People's Hospital of Wuxi, affiliated with Jiangnan University. Data were gathered from all hospitalized patients who met the diagnostic criteria for SARS-CoV-2 infection from December 1, 2022, to June 30, 2023. Patients were assigned into four groups receiving Nirmatrelvir/Ritonavir, Simnotrelvir/Ritonavir, Molnupiravir, and Azvudine, repectively.

Inclusion and Exclusion Criteria

Diagnosis Criteria

The diagnosis criteria were based on the "Diagnosis and Treatment Protocol for Novel Coronavirus Infection (Trial Version 10)" issued by the National Health Commission[4] (Figure 1).

Inclusion Criteria

1. Patients with mild (mainly upper respiratory tract infection symptoms, such as dry throat, cough, and fever.) or moderate (persistent fever >3 days or/and cough, dyspnea, but respiratory rate <30 times/min, and resting state oxygen saturation >93%; characteristic radiological findings of pneumonia caused by SARS-CoV-2 infection are visible) symptoms.
2. Age ≥ 18 years.
3. Patients only received Nirmatrelvir/Ritonavir, Simnotrelvir/Ritonavir tablets, Molnupiravir, or Azvudine as monotherapy for at least 2 consecutive days, in addition to basic disease management and symptomatic treatment.

Exclusion Criteria

1. Patients with severe (any of the following key indicators of deterioration: respiratory rate ≥30 times/min, oxygen saturation ≤93%, arterial partial pressure of oxygen/oxygen concentration ≤300mmHg without oxygen supplementation), rapid progression of clinical symptoms, rapid progression on radiologic imaging) or critical (respiratory failure requiring mechanical ventilation/shock/other organ failure) symptoms.
2. Age < 18 years.
3. Presence of severe comorbidities, such as acute myocardial infarction, acute cerebral hemorrhage, acute cerebral infarction, heart failure, liver or kidney function failure, human immunodeficiency virus infection, organ transplantation status, and patients undergoing treatment for malignant tumors.

Grouping and Treatment

Group-N: patients received Nirmatrelvir/Ritonavir tablets (150mg/100mg) orally every 12 hours for 5 days. Group-M: patients received Molnupiravir capsules (0.8g) orally every 12 hours for 5 days. Group-S: patients received Simnotrelvir/

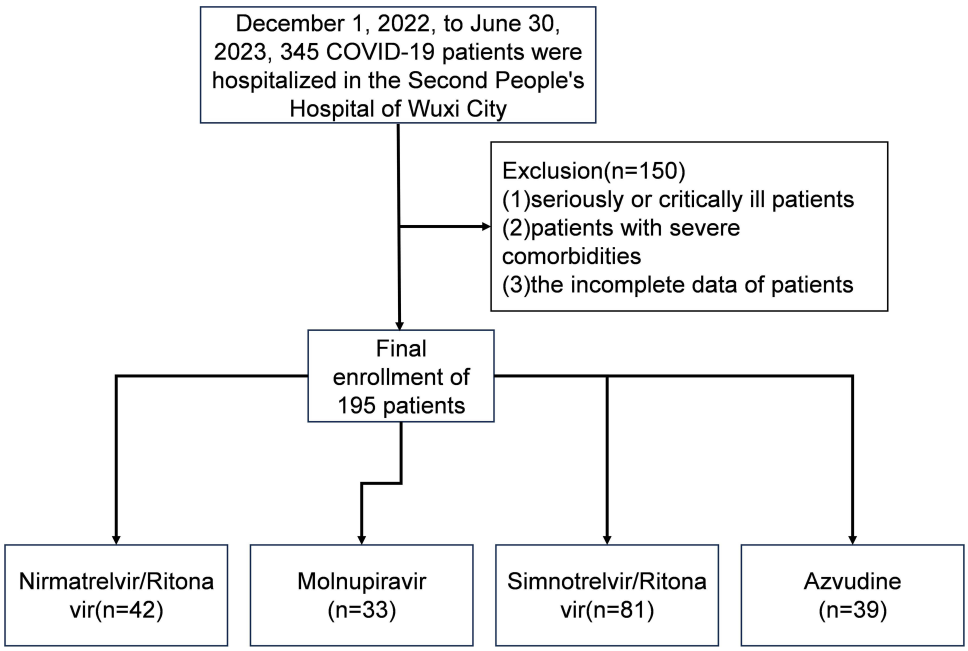

Figure 1 Flowchart of patient selection.

Ritonavir tablets (0.375g/0.1g) orally every 12 hours for 5 days. Group-A: patients received Azvudine tablets (5mg) orally once daily for up to 14 days.

Ethics Approval and Informed Consent

Ethics approval for this study was obtained from the Ethics Committee of the Second People's Hospital of Wuxi City, with approval number Y-25. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Prior to data collection, informed consent was obtained from all patients involved in the study. All patient data were handled confidentially and in compliance with relevant regulations and guidelines.

Data Collection

Standardized data collection forms were used to retrospectively extract patient information from electronic medical records and prescription systems. The collected information included demographic characteristics, basic information, diagnosis details, comorbidities, laboratory tests, concomitant medications, adverse reactions, etc. All data were independently reviewed by two physicians (LXY and WJH). All patients in the study were discharged after improvement. Patient discharge was considered as the study endpoint, and the length of hospital stay was recorded for each patient.

Statistical Analysis

Statistical analyses were conducted using R version 4.3.2 (R Foundation for Statistical Computing, www.r-project.org). Baseline characteristics of patients from each treatment group were compared. The Shapiro–Wilk test was used to assess the normality of the data distribution, and the Levene test was used to check for homogeneity of variances across different groups to determine appropriate statistical methods. For categorical variables, frequencies (n) and percentages (%) were utilized for descriptions, and either the chi-square test or Fisher's exact test was chosen for inter-group comparisons based on the distribution characteristics of the data. For continuous variables, data conformed to be a normal distribution were presented as means and standard deviations, while those not conformed were presented as medians and interquartile ranges. Either one-way ANOVA or the Kruskal–Wallis *H*-test was used to compare the difference between the four groups. Multiple linear regression analysis was adopted to explore the effects of comorbidities, concomitant medications, timing of treatment, gender, age, and lifestyle habits (smoking status) on the length of hospital stay. All statistical analyses were conducted with a significance level set at $P < 0.05$, indicating statistical significance.

Results

Demographic and Baseline Characteristics

During December 1, 2022, to June 30, 2023, 345 patients with COVID-19 were hospitalized in the Second People's Hospital of Wuxi. After screening, 195 patients receiving any of the oral antivirals were enrolled in this study: 42 received Nirmatrelvir/Ritonavir, 33 received Molnupiravir, 81 received Simnotrelvir/Ritonavir, and 39 received Azvudine (Figure 1). The baseline characteristics of patients in each treatment group was summarized in Table 1. No significant difference was observed in age, smoking status, BMI, comorbidity and concomitant medication between the four groups ($P > 0.05$). There was more proportion of male in Azvudine (71.79%), Simnotrelvir/Ritonavir (51.85%) and Nirmatrelvir/Ritonavir (52.38%) groups, while in Molnupiravir group, male accounted for 36.36% ($P = 0.026$). More patients started the early treatment within 5 days of symptom onset in Simnotrelvir/Ritonavir (48.15%), Nirmatrelvir/Ritonavir (52.38%) and Molnupiravir (42.42%) groups, compared to Azvudine (20.51%) group ($P = 0.015$).

Clinical Outcomes

Significant difference was observed in the duration of hospital stay between the four treatment groups ($P = 0.0113$), with median (IQR) of 9.0 (7.0–11.0) days in Group-S, 8.0 (6.0–11.0) days in Group-N, 10.0 (8.0–12.0) days in Group-M, 12.0 (8.0–14.5) days in Group-A (Figure 2 and Table 2). Patients receiving Nirmatrelvir/Ritonavir and Simnotrelvir/Ritonavir had significantly shorter hospital stays compared to those receiving Azvudine (*P(adj)* = 0.013, *P(adj)* = 0.039), as detailed in Table S1.

Table 1 Patient Characteristics

Group	S (n = 81)	N (n = 42)	M (n = 33)	A (n = 39)	*P* value
Age (y), mean ± SD	70.54±12.40	72.55±13.30	68.53±14.01	73.08±10.28	0.286
Gender (male), n (%)	42 (51.85%)	22 (52.38%)	12 (36.36%)	28 (71.79%)	0.026
Smoking, n (%)	9 (11.11%)	7 (16.67%)	4 (12.12%)	3 (7.70%)	0.583
BMI, mean ± SD	23.47±4.12	24.28±3.31	23.03±3.81	23.88±4.14	0.523
Comorbidities, n (%)	66 (81.48%)	35 (83.33%)	27 (81.82%)	32 (82.05%)	0.995
Concomitant medication, n (%)	60 (74.08%)	33 (78.57%)	24 (72.73%)	26 (66.67%)	0.681
Early treatment within 5 days of symptom onset, n (%)	39 (48.15%)	22 (52.38%)	14 (42.42%)	8 (20.51%)	0.015
Length of hospital stay (d), mean ± SD	9.70±4.71	8.86±3.54	10.03±3.72	11.56±4.38	0.037

Notes: Data are presented as n (%), mean (SD), or median (IQR). For continuous variables, unless otherwise stated, *P*-values were calculated using the *t*-test or Mann–Whitney *U*-test. For categorical variables, *P*-values were determined using the chi-square test, unless otherwise specified.
Abbreviations: S, Simnotrelvir/Ritonavir; N, Nirmatrelvir/Ritonavir; M, Molnupiravir; A, Azvudine; SD, standard deviation; IQR, interquartile range; y, years; SD, Standard Deviation; n, Number of participants; BMI: Body Mass Index; d, Days.

Stratified Analysis

Multivariate regression analysis was conducted to explore the impact of the following factors on hospital stays, including age, gender, smoking status, complication, concomitant medication, type of antivirals and timing of medication ($F = 4.538$, $P < 0.001$). Specifically, age ($P = 0.0002$) and type of antiviral drug received ($P = 0.004$) were found to be influencing factors for hospital stay (Figure 3).

Mechanism

Based on the mechanism of these four drugs, we divided the patients into 3CLpro inhibitor (Nirmatrelvir/Ritonavir and Simnotrelvir/Ritonavir, n = 123), and RdRp inhibitor (Molnupiravir and Azvudine, n = 72) groups for further analysis. The median (IQR) hospital stays of 3CL and RdRp groups was 9 (6–11) days and 11 (8–13) days, respectively (Figure 4A). Patients in 3CL group had significantly shorter hospital stay compared to that in RdRp group ($P = 0.0032$), as shown in Table S2.

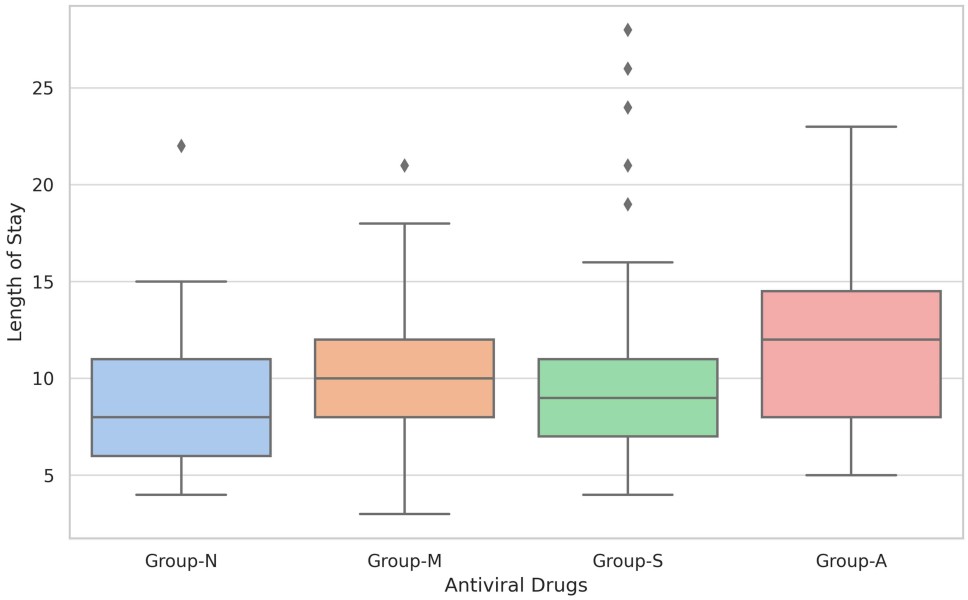

Figure 2 The distribution of length of hospital stay for patients.
Notes: *$p < 0.05$, indicating a statistically significant difference between the two groups. In this figure, the statistical significance is marked above the boxplots.

Table 2 Statistical Analysis of Length of Hospital Stay Across Patient Groups (Days)

Group	Mean	Min	Max	Mid	SD
N	8.86	4	22	8	3.54
M	10	3	10	21	3.72
S	9.7	4	28	9	4.71
A	11.6	5	23	12	4.38

Abbreviations: S, Simnotrelvir/Ritonavir; N, Nirmatrelvir/Ritonavir; M, Molnupiravir; A, Azvudine; SD, standard deviation; Min, Minimum; Max, Maximum; Mid, Median.

Timing of Medication

We observed a statistically significant difference in the timing of medication among the four groups of patients (P = 0.015), with patients in Nirmatrelvir/Ritonavir group receiving medication more promptly, whereas patients in Azvudine group initiated treatment later (Table 1). Propensity score matching analysis was used, which included patient demographics, comorbidities, concomitant medications, and drug types as covariates. The impact of early (within 5 days of symptom onset, n = 83) versus late (>5 days of symptom onset, n = 112) medication initiation on hospitalization duration was explored. No significant difference in hospitalization duration was observed between early and late medication initiation among hospitalized patients with COVID-19 (P = 0.1109) (Figure 4B and Table S3).

Age

Patients aged ≤65 years exhibited shorter hospitalization duration compared to those >65 years old [median (IQR), 7.5 (6.0–9.3) days vs 10 (8.0–12.0) days, (P = 0.0010)]. In population >65 years old, the hospital stays were significantly shorter in Nirmatrelvir/Ritonavir and Simnotrelvir/Ritonavir groups, compared to that in Azvudine group (P = 0.0420,

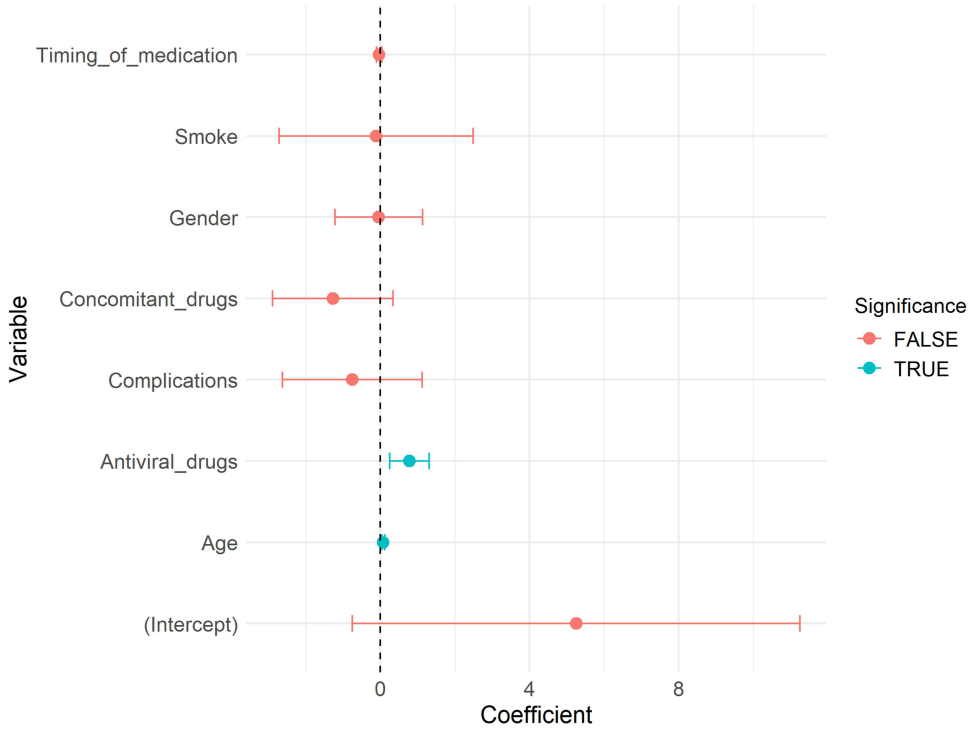

Figure 3 Impact of Covariates on Length of Hospital Stay.

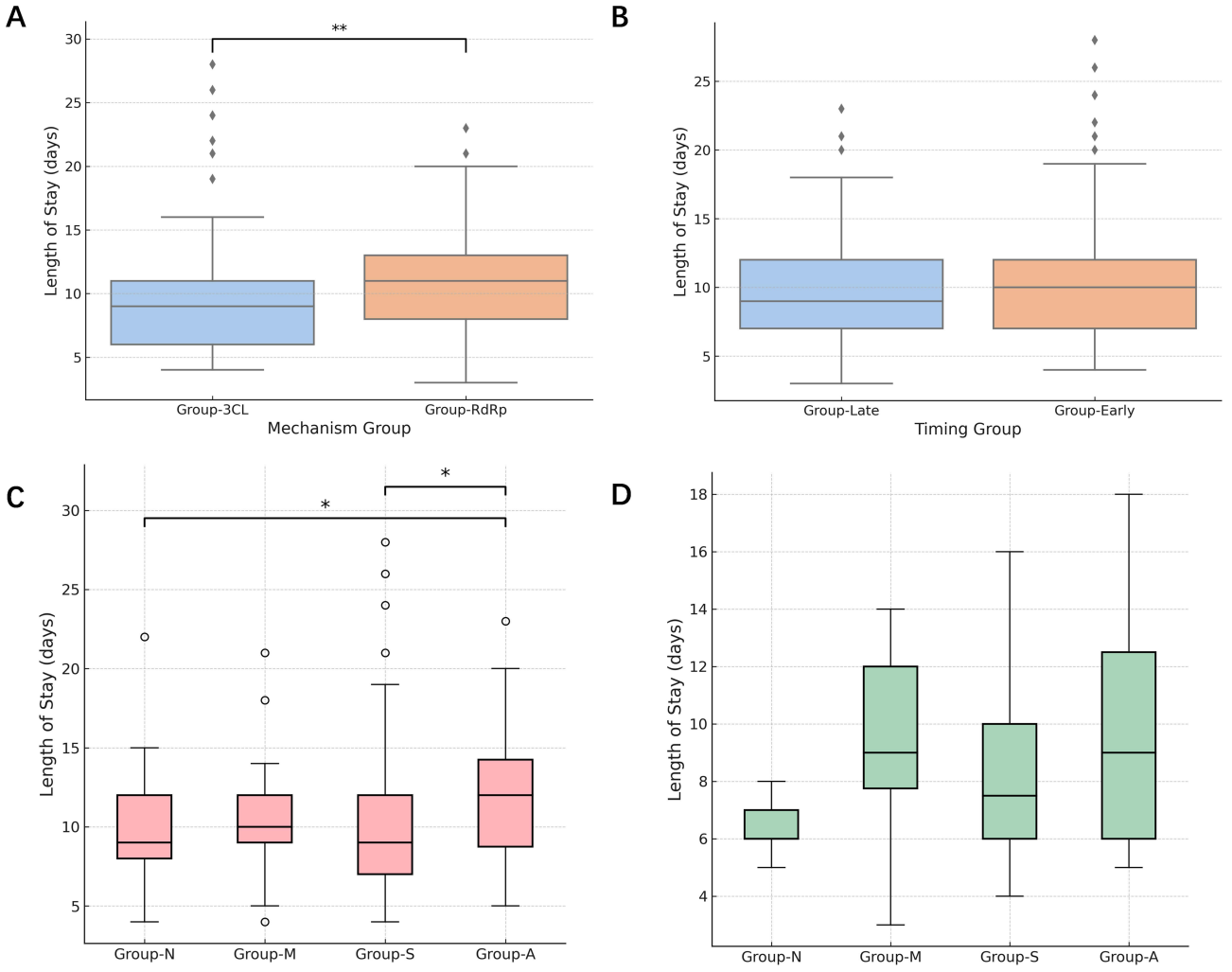

Figure 4 Distribution of Hospital Stay Duration (Day) among Different Subgroups of Patients.
Notes: (**A**) Length of hospitalization of patients in subgroups according to mechanism. Group-3CL: patients use Simnotrelvir/Ritonavir or Nirmatrelvir/Ritonavir, Group-RdRp: patients use Azvudine, and Molnupiravir. (**B**) Length of hospitalization of patients in subgroups according to timing of medication, with medication within 5 days after the onset of symptoms being considered early, and greater than 5 days being considered late. (**C**) Length of hospitalization of patients >65 years of age. (**D**) Length of hospitalization of patients ≤65 years of age for patients. *p < 0.05, indicating a statistically significant difference between the two groups. **p < 0.01, indicating a highly significant difference between the two groups. In this figure, the statistical significance is marked above the boxplots. Group-A: Azvudine group, Group-M: Molnupiravir group, Group-N: Nirmatrelvir/ritonavir group, Group-S: Simnotrelvir/Ritonavir group.

P = 0.0232) (Figure 4C). However, no significant difference was observed in hospital stays between different treating groups in patients ≤65 years of age (Figure 4D and Tables S4–S7).

Comorbidity

In this study, patients presented with comorbidities were administrated with symptomatic treatment. Neither cardiac dysfunction was observed in patients with heart disease, nor significant renal abnormalities were noted in those with kidney disease. Patients with comorbid rheumatic immune diseases, thyroid diseases, solid tumors, and respiratory system diseases remained clinically stable under specialized symptomatic treatment. In subgroup with comorbidity, differences in hospitalization duration were observed between different antiviral groups [median (IQR): 9.0 (6.0–11.0) days in Nirmatrelvir/Ritonavir group, 10.0 (8.0–12.0) days in Molnupiravir group, 9.0 (7.0–11.0) days in Simnotrelvir/Ritonavir group, 12.0 (8.0–14.5) days in Azvudine group; P = 0.0400]. Dunn's test for pairwise comparison showed that the hospitalization duration in patients receiving Nirmatrelvir/Ritonavir was significantly shorter than that in Azvudine group (P = 0.0185) (Tables S8 and S9).

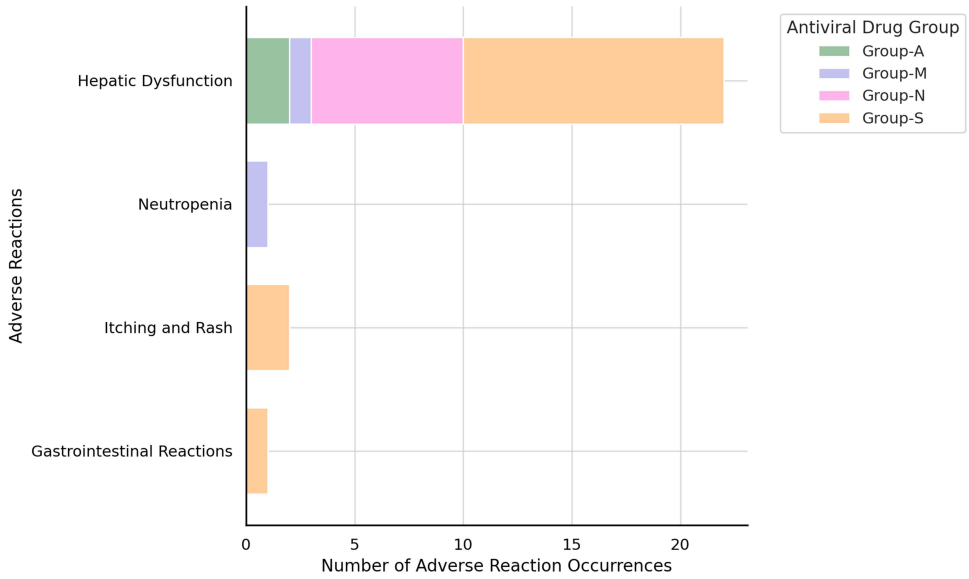

Figure 5 Comparison of Adverse Reactions Across Different Antiviral Drug Groups.
Notes: Group-A: Azvudine group, Group-M: Molnupiravir group, Group-N: Nirmatrelvir/ritonavir group, Group-S: Simnotrelvir/Ritonavir group.

Concomitant Medication

During treatment period, patients with drug contraindication were either temporarily substituted with alternative medications or discontinued the antiviral therapy. Among patients with concomitant medication, the median (IQR) hospitalization duration revealed no significant differences between the four treatment groups [Nirmatrelvir/Ritonavir: 9.0 (7.0–12.0) days, Molnupiravir: 10.0 (8.8–12.0) days, Simnotrelvir/Ritonavir group: 9.5 (8.0–12.0) days, Azvudine: 12.0 (8.0–14.8) days, $P = 0.1300$] (Table S10).

Safety

Adverse Reactions

As of safety outcome, adverse events were reported in 2/33 (6.1%), 7/42 (16.7%), 16/81 (19.8%) and 2/39 (5.1%) cases from Molnupiravir, Nirmatrelvir/Ritonavir, Simnotrelvir/Ritonavir and Azvudine groups, respectively. In Molnupiravir group, 1 case (3.0%) of hepatic dysfunction and 1 case (3.0%) of leukopenia were observed. In Nirmatrelvir/Ritonavir group, hepatic dysfunction was noted in 7 cases (16.7%). Typically, any abnormalities in hepatic function indicators, including Alanine Aminotransferase, Aspartate transaminase and bilirubin levels, are documented by the attending physicians along with the corresponding management strategies. Notably, one patient had pre-existing liver disease, but there was no significant change in liver function indicators following antiviral drug treatment. In Simnotrelvir/Ritonavir group, 12 cases (14.8%) exerted hepatic dysfunction, including 2 patients with pre-existing liver disease. Additionally, 1 case (1.2%) of gastrointestinal reactions and 2 cases (2.4%) of rash and itching were observed. In Azvudine group, 2 cases (5.1%) of hepatic dysfunction were observed. The severity of adverse events across all four groups ranged from grades 1 to 2, and no serious adverse events related to the drugs were reported during the study (Figure 5).

Discussion

This study indicated Simnotrelvir/Ritonavir and Nirmatrelvir/Ritonavir were more potent in shortening the hospital stay of hospitalized patients with COVID-19 compared to Azvudine during Omicron wave. No significant differences in duration of hospital stay were observed in term of early or late treatment timing, with or without comorbidity, or concurrent medication use. In particular, for patients with liver diseases and relatively poor conditions at baseline, oral administration of Simnotrelvir/Ritonavir did not result in obvious change of indicator of liver function. No serious adverse events were recorded in any treatment group throughout the study. RdRp inhibitors disrupt viral replication by

introducing erroneous nucleotides into newly synthesized RNA molecules through binding to the RNA polymerase of SARS-CoV-2.[15] 3CL protease is a crucial enzyme for the replication of SARS-CoV-2 and is highly conserved, making it an important target for drug development.[17,18] In our study patients treated with 3CL protease inhibitors had significantly shorter hospital stays compared to those treated with RdRp inhibitors.[19] This suggests drugs targeting 3CL protease inhibitors may have better potential for the treatment of hospitalized COVID-19 patients. This study is the first to compare the effectiveness and safety of Simnotrelvir/Ritonavir, the first Chinese-developed 3CL protease inhibitor, head-to-head with three widely used antiviral drugs.[20]

According to both Chinese and international treatment guidelines, initiating antiviral therapy within five days of symptom onset is more effective.[21,22] However, our data revealed no significant difference in hospital stay durations between early and late medication initiation. Instead of ruling out the potential benefits of early treatment, our findings suggest that patients who missed the optimal treatment window should still receive antiviral therapy promptly after symptom onset to reduce viral load and mitigate the risk of developing "Long COVID". "Long COVID" refers to multisystemic symptoms after SARS-CoV-2 infection persisting for at least two months, including fatigue, dyspnea, and loss of taste or smell, which remains unexplained.[23] It affects an estimated 50–70% of hospitalized patients.[24] The substantial impact and complex disease mechanisms make long COVID a significant challenge for the global medical community, with some studies suggesting that persistent viral presence may be a driving factor for long-term symptoms.[25] Hence, oral antiviral drugs may play a crucial role in combating long COVID, although this hypothesis requires further investigation. According to the latest expert consensus on the clinical application of anti-neocoronavirus small molecule drugs,[26] it is recommended that the long neocoronavirus population may choose anti-neocoronavirus small molecule drugs as appropriate along with symptomatic treatment.

Given that most studies have focused on non-hospitalized, younger patients, our study included predominantly elderly hospitalized patients with an average age of 71 years. Advanced age has consistently been identified as a significant risk factor for COVID-19,[27] with older patients often experiencing more severe illnesses, poorer prognosis, and higher mortality rates. Some studies have noted a significant correlation between COVID-19 and aging, with notable up-regulation of aging markers in the lung cells of elderly COVID-19 patients.[28] Therefore, evaluating the efficacy and safety of oral small-molecule antiviral therapy in elderly patients is crucial. Our study observed no severe adverse events following medication in elderly patients, confirming the safety of the four drugs. Additionally, a stratified analysis by age revealed significantly shorter hospital stays among patients aged >65 years receiving Simnotrelvir/Ritonavir and Nirmatrelvir/Ritonavir treatment compared to the Azvudine group, suggesting that 3CL inhibitors may offer better treatment outcomes for elderly patients under the premise of excluding contraindications and ensuring tolerance to antiviral therapy. Our research represents an innovative exploration of antiviral drug use in elderly patients, albeit limited by sample size, indicating the need for further in-depth studies in this area.

In this study, no significant adverse effects were observed in patients with comorbidities or elderly individuals receiving oral small-molecule antiviral drugs. Following the exclusion of contraindicated combination medications explicitly mentioned in the drug instructions, patients with other combination medications and one or more comorbidities, as well as those with relatively poorer baseline conditions, can still be treated for COVID-19 with oral antiviral drugs.

Previous studies have noted that the common adverse reactions to Molnupiravir including diarrhea, nausea, and dizziness, are generally mild to moderate, and it is not a substrate for specific hepatic enzymes and transporters, exhibiting no known adverse drug interactions 5. Adverse reactions to Azvudine predominantly include fever, headache, dizziness, nausea, and vomiting, all of grade 1 severity. Caution is advised when used concomitantly with P-glycoprotein (P-gp) substrate drugs, P-gp inhibitors, or P-gp inducers, and blood drug concentrations should be monitored as necessary, with dose adjustments made as appropriate. No significant adverse effects have been observed in patients with underlying diseases or in elderly patients.[8] Common adverse reactions to Nirmatrelvir/Ritonavir include taste disturbances, diarrhea, increased fibrin D-dimer, elevated alanine aminotransferase levels, headaches, nausea, and vomiting.[9] Adverse events in clinical studies of Simnotrelvir/Ritonavir mainly include elevated blood triglyceride levels, decreased neutrophil counts, and diarrhea.[11] Both 3CLpro inhibitors have contraindications for concomitant use with

certain medications metabolized by CYP3A, although previous studies have demonstrated good safety profiles for all four drugs.

In our data, the primary adverse reaction observed was hepatic dysfunction. Previous studies have demonstrated that hepatic function damage can be observed in COVID-19 patients and may lead to poor prognosis in severe COVID-19 patients or those with pre-existing liver disease. Therefore, the hepatic dysfunction observed in this study cannot rule out immune damage caused by inflammatory reactions or cytopathic effects induced by the virus, and its causality with the use of antiviral drugs cannot be determined. However, it has been reported that Molnupiravir has a relatively minor impact on liver function impairment.[29] A real-world data study observed a significant decrease in alanine transaminase and aspartate transaminase levels compared to baseline in patients treated with Azvudine, but causality could not be clearly established.[30]

Retrospective studies may exhibit literature bias, particularly with mild safety events that are difficult to distinguish from COVID-19 signs and symptoms. However, as all included patients were hospitalized, enabling continuous monitoring of their signs, symptoms, and disease progression, serious adverse events (SAEs) could be noted. The relatively short duration of antiviral therapy for COVID-19 (usually 5–7 days) also reduces the risk of safety event development.

This study has certain limitations: (1) Reliance on real-world data from a single hospital, which limits its external validity and generalizability. (2) The lack of a prospective design and randomization, which could omit important confounding factors. However, constrained by the circumstances of the COVID-19 pandemic that time and the relatively poor health status of hospitalized patients, all patients strictly adhered to the Chinese Diagnosis and Treatment Guidelines for COVID-19, receiving antiviral drug treatment. (3) Bias may exist in the collection and recording of symptom manifestations and time points from patient medical records, potentially affecting the accuracy of the results. (4) Limited endpoint selection with a single dimension for evaluating efficacy. Due to the large number of patients then and the shortage of medical resources, the data for secondary endpoints were insufficient.

In summary, we conducted the first real-world comparison of the efficacies of Simnotrelvir/Ritonavir, Nirmatrelvir/Ritonavir, Azvudine, and Molnupiravir by examining average hospital stay durations across different patient groups. We recorded and analyzed adverse reactions to assess drug safety. Our analyses provide evidence of the efficacy and safety of these four drugs in treating COVID-19, aiding in clinical decision-making and improving treatment outcomes for hospitalized patients. Additionally, our study demonstrates that oral small molecule antiviral drugs can be effective for COVID-19 patients who were unable to receive early treatment, including those with comorbidities or those using non-contraindicated combination drugs. Importantly, no severe adverse reactions were recorded. Further enhancement of our comparative analysis with more indicators would benefit from additional large-scale real-world studies.

Conclusion

This study is the first to use real-world data to compare the duration of hospital stay and safety profiles of major oral antivirals, thereby contributing to the optimization of COVID-19 treatment strategies in hospitalized patients. Simnotrelvir/Ritonavir and Nirmatrelvir/Ritonavir demonstrated particular benefits for patients aged 65 and older. Even when antiviral treatment is delayed, patients may still derive therapeutic benefits. Furthermore, these oral antivirals have shown a favorable safety profile in patients without contraindicated comorbidities or co-administered medications.

Data Sharing Statement

Data related to this research can be obtained from the corresponding author if requested reasonably.

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Disclosure

The authors report no conflicts of interest in this work.

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