Infection and Drug Resistance

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ORIGINAL RESEARCH

Comparison of Azvudine and Nirmatrelvir/Ritonavir and Combined Use in Patients with COVID-19

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Purpose: To compare the effectiveness of azvudine and nirmatrelvir/ritonavir for the treatment of coronavirus disease (COVID-19).

Patients and Methods: We conducted a retrospective analysis of data from 576 patients with COVID-19, comprising 195 patients without antiviral therapy, 226 patients treated with azvudine, 114 patients treated with nirmatrelvir/ritonavir, and 41 patients were treated with azvudine and nirmatrelvir/ritonavir concurrently. We compared their symptoms, mortality rates, and the length and cost of hospitalization.

Results: The incidence of symptoms was similar in patients treated with azvudine and in those treated with nirmatrelvir/ritonavir. However, among patients experiencing weakness, the duration of weakness was significantly shorter in the azvudine group than in the nirmatrelvir/ritonavir group (P=0.029). Mortality did not differ significantly between the azvudine group and the nirmatrelvir/ritonavir group (18.14% vs.10.53%, P=0.068). Among "severe patients", the mortality rate was markedly lower in patients treated with nirmatrelvir/ritonavir than in patients treated with azvudine (16.92% vs.32.17%, P=0.026). In patients with hepatic insufficiency, those treated with nirmatrelvir/ritonavir had substantially lower mortality than those treated with azvudine (15.09% vs.34.25%, P=0.016). In addition, patients treated with nirmatrelvir/ritonavir had longer hospital stays (P=0.002) and higher hospital costs (P<0.001) than those receiving azvudine. Compared with patients treated with nirmatrelvir/ritonavir or azvudine alone, patients taking nirmatrelvir/ritonavir and azvudine concurrently had no significant improvement in survival (P>0.05), length of stay (P>0.05), or hospital costs (P>0.05).

Conclusion: Azvudine is recommended for patients with non-severe COVID-19 with weakness. Nirmatrelvir/ritonavir is recommended for patients with severe COVID-19, to reduce mortality, and it could be the best choice for patients with hepatic insufficiency. The concurrent use of nirmatrelvir/ritonavir and azvudine in patients with COVID-19 could be not recommended.

Keywords: azvudine, nirmatrelvir/ritonavir, COVID-19, SARS-CoV-2

Introduction

Azvudine and nirmatrelvir/ritonavir are the two most commonly used antiviral drugs for treating COVID-19 in China. Previous studies have shown that both azvudine and nirmatrelvir/ritonavir are effective antiviral treatments for COVID-19.[1–3] However, few studies have compared the effectiveness of azvudine and nirmatrelvir/ritonavir for COVID-19 treatment.

Azvudine was authorised for COVID-19 treatment by the State Drug Administration of China on 25 July 2022, and subsequently included in the Diagnosis and Treatment Program for Novel Coronavirus Pneumonia (Ninth Edition) on 9 August 2022.[4] Azvudine is a nucleoside analogue with broad-spectrum antiviral activity. Its metabolites are embedded in viral RNA during SARS-CoV-2 RNA synthesis, thereby treating COVID-19 by inhibiting viral replication.[5] Azvudine can shorten the time for the first nucleic acid test to turn negative, reduce the duration of symptoms in patients with moderate COVID-19, improve clinical manifestations, and lower the incidence of disease progression.[1,6]

Received: 31 July 2023
Accepted: 29 November 2023
Published: 22 December 2023

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In December 2021, the US Food and Drug Administration (FDA) granted Emergency Use Authorisation for the use of nirmatrelvir/ritonavir to treat patients with COVID-19 with a high risk of progressing to severe disease.[7] On 25 May 2023, the FDA officially approved nirmatrelvir/ritonavir for treating COVID-19 in adults in the USA. Nirmatrelvir is a peptidomimetic inhibitor that prevents viral replication by inhibiting SARS-CoV-2 main protease (Mpro) so that it cannot process polyprotein precursors; ritonavir is an HIV-1 protease inhibitor that slows down metabolism of nirmatrelvir by inhibiting CYP3A4, thereby providing higher systemic exposure.[8] A previous study demonstrated that nirmatrelvir/ritonavir effectively reduced mortality and the time to PCR-negative conversion in patients with COVID-19.[9] Additionally, nirmatrelvir/ritonavir substantially reduced hospitalisation rates in patients with COVID-19.[10]

Currently, few studies are available that compare the effectiveness of azvudine and nirmatrelvir/ritonavir in patients with COVID-19. Both drugs appear to have unique advantages for treating COVID-19. Compared with those treated with azvudine, patients treated with nirmatrelvir/ritonavir tend to achieve faster first negative nucleic acid conversion.[11] However, in patients with comorbidities, azvudine is associated with a lower risk of composite disease progression than nirmatrelvir/ritonavir is.[12] Choosing between azvudine and nirmatrelvir/ritonavir for COVID-19 treatment poses a clinical challenge, necessitating a comprehensive discussion and comparison of their relative effectiveness. Therefore, in this retrospective study, we aimed to better understand the treatment choice between nirmatrelvir/ritonavir and azvudine in patients with COVID-19 who received either or both treatments.

Materials and Methods

Patient Cohort and Study Design

We conducted a retrospective cohort study on 664 patients with COVID-19. The inclusion criteria were: (1) Patients hospitalized at Guangzhou First People's Hospital owing to SARS-CoV-2 infection between June 2022 and January 2023 and (2) patients able to accurately express their discomfort during hospitalization. The exclusion criteria were: (1) Patients with an unknown vaccination history; (2) patients co-infected with other respiratory viruses; (3) patients with incomplete data. We excluded 88 patients who did not meet the eligibility criteria and included 576 patients in the analysis. Among these patients, 195 did not receive antiviral therapy and were assigned to the control group, 226 were treated with azvudine and assigned to the azvudine group, 114 were treated with nirmatrelvir/ritonavir and assigned to the nirmatrelvir/ritonavir group, and 41 were treated with both azvudine and nirmatrelvir/ritonavir. A flowchart of the patient selection process is presented in Figure 1. We started follow-up on the date of admission to hospital with confirmed COVID-19. If the patient did not return to the hospital for a follow-up visit after discharge, follow-up ended on the date of discharge. If the patient returned to the hospital for follow-up visit within 1 month after discharge, the follow-up time

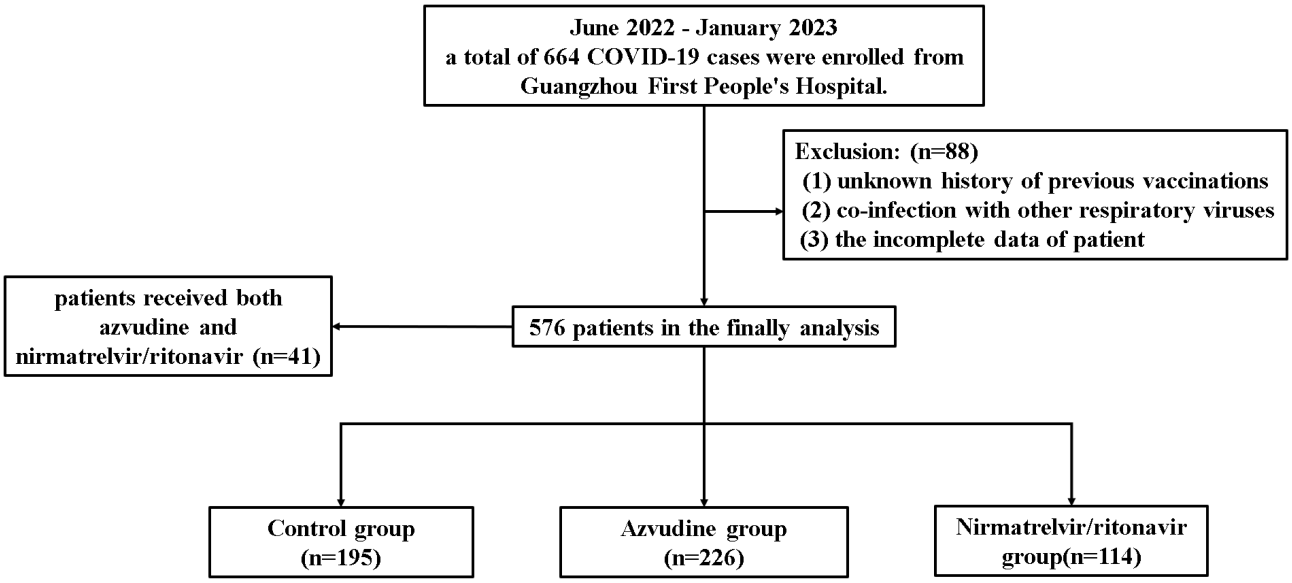

Figure 1 Flowchart of patient selection.

was extended to the date of the first follow-up visit. The median (IQR) overall length of hospital stay was 9 (6–14) days. The overall median (IQR) follow-up period was 12 (8–18) days.

Definitions

According to the US National Institutes of Health (NIH) COVID-19 Treatment Guidelines,[13] COVID-19 severity was grouped into asymptomatic or presymptomatic infection, mild illness, moderate illness, severe illness, and critical illness. In our study, patients with asymptomatic or presymptomatic infection, mild illness, and moderate illness were defined as "non-severe patients", and those with severe illness and critical illness were defined as "severe patients".

Antiviral Treatment

Azvudine was administered as 5 mg once daily for up to 14 days. Nirmatrelvir 300 mg and ritonavir 100 mg were administered twice daily for 5 days. In patients with moderate renal insufficiency, a reduced dose of nirmatrelvir 150 mg and ritonavir 100 mg twice daily for 5 days was administered at the attending doctor's discretion.[14]

Ethics Approval and Informed Consent

The authors confirm that all procedures undertaken in this study adhere to the ethical standards set by the appropriate national and institutional committees on human experimentation, as well as the Helsinki Declaration of 1975, with its 2008 revisions. The retrospective analysis conducted in this study received approval from the Medical Ethics Committee of Guangzhou First People's Hospital (Approval number: K-2023-066-01). All data in this study were de-identified and anonymized. A waiver of informed consent was granted as all anonymized data was collected retrospectively in accordance with the ethics approval.

Data Collection

We collected comprehensive data from Guangzhou First People's Hospital for each COVID-19 patient, which included detailed information on demographics, epidemiology, comorbidities, symptoms, imaging reports (initial results upon admission), laboratory test results (initial results upon admission), treatment, and outcomes. The study endpoint was defined as either death or discharge from Guangzhou First People's Hospital. A dedicated team of physicians and researchers collaborated to crosscheck and verify the accuracy of patient data.

Statistical Analyses

Statistical analyses were performed using SPSS Version 25.0 (IBM, Armonk, New York, USA). As the Shapiro–Wilk normality test indicated that none of the continuous variables in this study followed a normal distribution, these variables were presented as median values with interquartile ranges. Categorical variables were presented as frequencies and percentages. Group comparisons for continuous variables were conducted using the Mann–Whitney *U*-test, whereas categorical variables were assessed using the chi-squared or Fisher's exact test. Survival analysis was employed to compare the duration of symptoms, with group comparisons performed using the Log rank test. All statistical tests were two-sided, and $P< 0.05$ was considered statistically significant.

SPSS Version 25.0 (IBM, Armonk, New York, USA) and GraphPad Prism version 8.0.0 (GraphPad Software, San Diego, California USA) were used to generate figures.

Results

Patient Characteristics and the Control of Confounding Factors

Considering that variations among the patients in clinical characteristics and laboratory test results may influence the efficacy evaluation comparison between azvudine and nirmatrelvir/ritonavir, we collected and analysed the clinical characteristics and laboratory test results of the patients to control for confounding factors in the results.

As shown in Table 1, there were no significant differences in age (P=0.433); sex (P=0.240); COVID-19 vaccination status (P=0.540); comorbidities such as hypertension (P=0.991), diabetes (P=0.103), coronary heart disease (P=0.620), hepatitis (P=0.174), chronic obstructive pulmonary disease (P=0.150), and chronic kidney disease (P=0.689); severity at

Table 1 Patient Characteristics in the Azvudine Group and the Nirmatrelvir/Ritonavir Group

	Azvudine Group(n=226)	Nirmatrelvir/Ritonavir Group(n=114)	*p*
Age	78(68–86)	78(68–87)	0.433
Sex			0.240
Men	140(62%)	78(68%)	
Women	86(38%)	36(32%)	
COVID-19 vaccination status			0.540
Vaccinated	115(51%)	54(47%)	
None	111(49%)	60(53%)	
Comorbidities			
Hypertension	129(57%)	65(57%)	0.991
Diabetes	60(27%)	40(35%)	0.103
Coronary heart disease	52(23%)	29(25%)	0.620
Hepatitis	9(4%)	1(1%)	0.174
Chronic obstructive pulmonary disease	17(8%)	14(12%)	0.150
Chronic kidney disease	25(11%)	11(10%)	0.689
Severity at admission			0.169
Non-severe	111(49%)	49(43%)	
Severe	115(51%)	65(57%)	
Treatments			
Systemic steroid	152(67%)	84(74%)	0.225
Antibiotic	204(90%)	99(87%)	0.339

admission (*P*=0.169); or treatments such as systemic steroid (*P*=0.225) and antibiotic (*P*=0.339) uses between the azvudine and nirmatrelvir/ritonavir groups. Since there were no significant differences in confounding factors between the two groups, we believe that these factors would not impact the results, thereby increasing the reliability of our findings.

There were no significant differences in C-reactive protein levels (*P*=0.596), white blood cell (WBC) count (*P*=0.441), lymphocyte levels (*P*=0.126), monocyte levels (*P*=0.917), neutrophil percentage (*P*=0.462), total bilirubin levels (*P*=0.407), direct bilirubin levels (*P*=0.607), indirect bilirubin levels (*P*=0.729), creatinine levels (*P*=0.378), urea nitrogen levels (*P*=0.909), aspartate transaminase levels (*P*=0.097), or albumin levels (*P*=0.070) between the azvudine and nirmatrelvir/ritonavir groups (Table 2). Hence, we do not believe that these confounding factors would affect our findings.

Supplementary Table 1 presents a detailed comparison between the azvudine and control groups, which did not yield any substantial differences, except for the use of hormones and monocyte levels. Similarly, Supplementary Table 2 details the comparison between the nirmatrelvir/ritonavir and control groups, which also did not exhibit any notable differences, except for the use of hormones and lymphocyte levels.

Table 2 The Laboratory Test Results in the Azvudine Group and the Nirmatrelvir/Ritonavir Group

	Azvudine Group (n=226)	Nirmatrelvir/Ritonavir Group (n=114)	*p*
C-reactive protein (mg/L)	52.6(15.7–112.9)	51.0(16.3–95.0)	0.596
White blood cell count (10^9/L)			0.441
<4	21(9%)	12(10%)	
4–10	154(68%)	83(73%)	
>10	51(23%)	19(17%)	

(*Continued*)

Table 2 (Continued).

	Azvudine Group (n=226)	Nirmatrelvir/Ritonavir Group (n=114)	*p*
Lymphocyte count(10^9/L)	0.96(0.57–1.38)	0.80(0.57–1.23)	0.126
Monocyte count(10^9/L)	0.52(0.36–0.76)	0.53(0.33–0.78)	0.917
Neutrophil percentage(%)	77.73(68.69–86.18)	77.86(65.76–86.53)	0.462
Total bilirubin(μmol/L)	10.7(8.6–14.4)	10.5(7.8–14.2)	0.407
Creatinine(μmol/L)	83(67–120)	84(62–106)	0.378
Urea(mmol/L)	6.53(4.62–10.25)	6.56(5.13–9.38)	0.909
Aspartate transaminase(U/L)	29(21–44)	33(22–51)	0.097
Direct bilirubin(μmol/L)	2.4(1.6–3.5)	2.2(1.5–3.8)	0.607
Indirect bilirubin(μmol/L)	8.3(6.3–10.9)	8.3(6.1–10.4)	0.729
Albumin(g/L)			0.070
<35	159(70%)	91(80%)	
≥35	67(30%)	23(20%)	

Comparison of Efficacy Between Azvudine and Nirmatrelvir/Ritonavir in Patients with COVID-19

Figure 2 shows that there were no significant differences in the incidence of cough (*P*=0.745), fever (*P*=0.415), myalgia (*P*=0.362), pharyngitis (*P*=0.170), weakness (*P*=0.212), and shortness of breath (*P*=0.922) between the azvudine and nirmatrelvir/ritonavir groups. This indicates that nirmatrelvir/ritonavir did not reduce the occurrence of COVID-19 symptoms compared to azvudine. Supplementary Figure 1 demonstrates that within the azvudine and nirmatrelvir/ritonavir groups, if patients developed fever, there was no significant difference in their maximum body temperature (*P*=0.123).

Furthermore, when patients experienced symptoms, the azvudine group exhibited no significant differences in the duration of cough (*P*=0.344), fever (*P*=0.932), myalgia (*P*=0.493), pharyngitis (*P*=0.999), or shortness of breath (*P*=0.076) compared to the nirmatrelvir/ritonavir group. However, the azvudine group had a significantly shorter duration of weakness (*P*=0.029) as shown in Figure 3.

Finally, we compared the mortality rates between the azvudine and nirmatrelvir/ritonavir groups (Figure 4). There was no significant difference in mortality between the azvudine and nirmatrelvir/ritonavir groups (*P*=0.068). However, among severe patients, the azvudine group had a significantly higher mortality rate than the nirmatrelvir/ritonavir group (*P*=0.026). Additionally, subgroup analysis results revealed that among the patients with renal insufficiency, there was no significant difference in mortality between the azvudine and nirmatrelvir/ritonavir groups (*P*=0.175). However, among patients with hepatic insufficiency, the nirmatrelvir/ritonavir group exhibited a lower mortality rate (*P*=0.016).

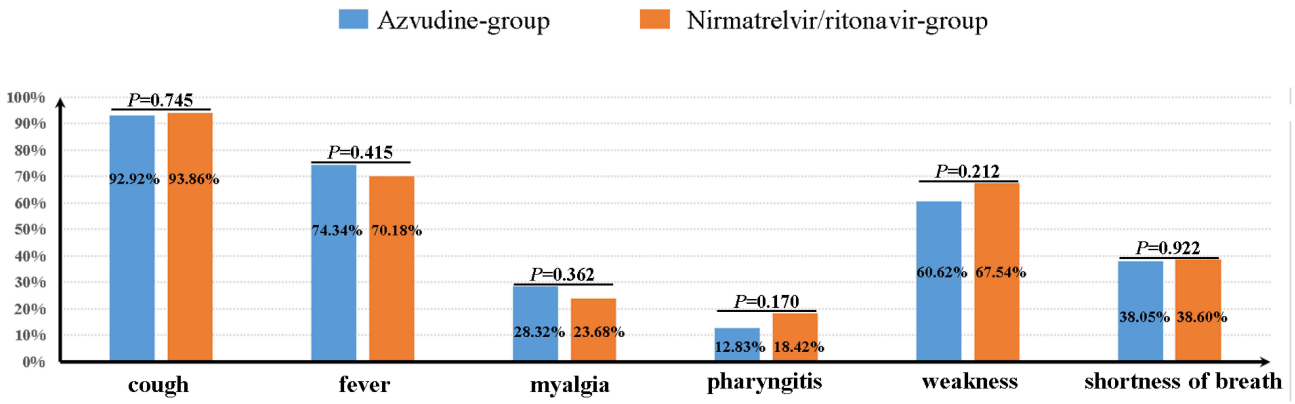

Figure 2 Comparison of the incidence of cough, fever, myalgia, pharyngitis, weakness, and shortness of breath in the azvudine and nirmatrelvir/ritonavir groups.

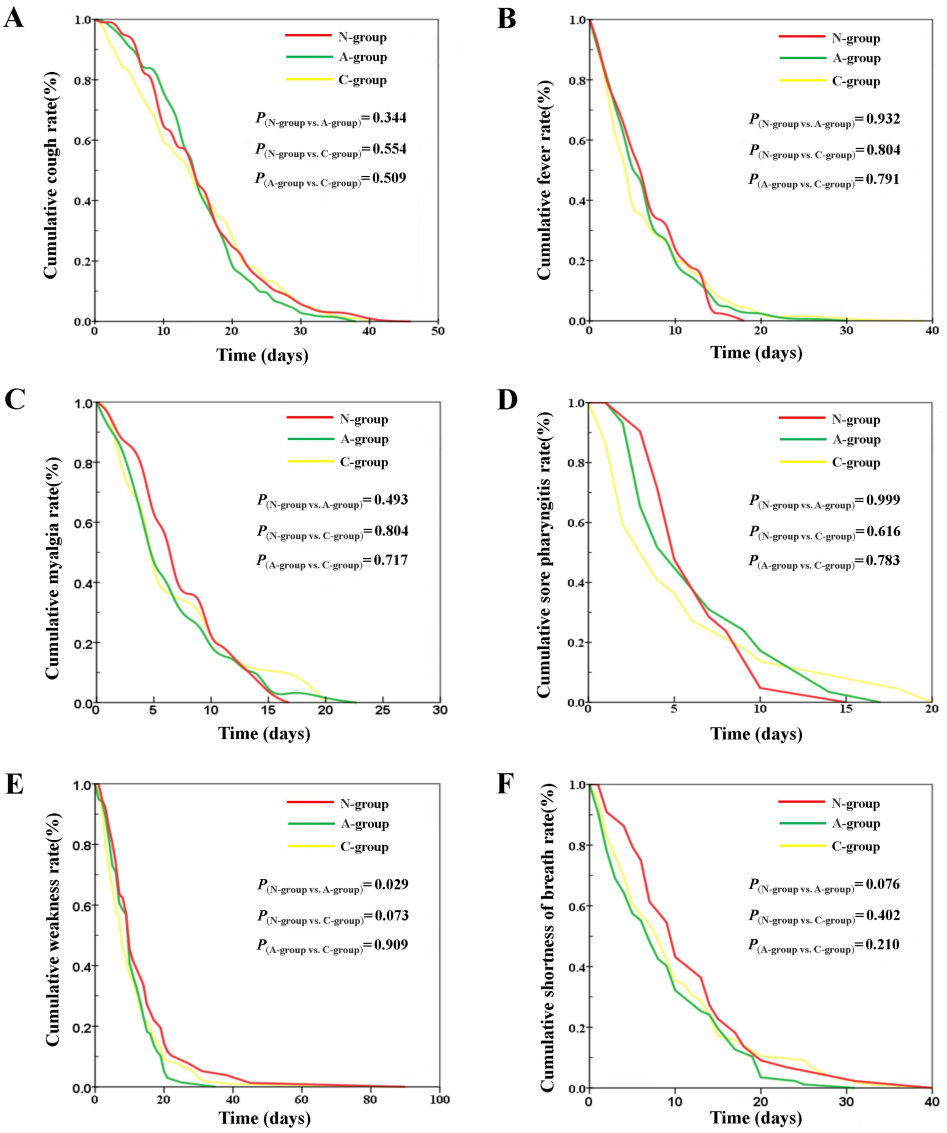

Figure 3 The duration of cough, fever, myalgia, pharyngitis, weakness, and shortness of breath in the azvudine, nirmatrelvir/ritonavir, and control (no antiviral therapy) groups.

Notes: (**A**) The duration of cough by treatment group. (**B**) The duration of fever by treatment group. (**C**) The duration of myalgia by treatment group. (**D**) The duration of pharyngitis by treatment group. (**E**) The duration of weakness by treatment group. (**F**) The duration of shortness of breath by treatment group. N-group: nirmatrelvir/ritonavir group; A-group: azvudine group; C-group: control group.

In addition, we compared the length of hospital stay and hospital expenses between the azvudine and nirmatrelvir/ritonavir groups. We found that patients in the nirmatrelvir/ritonavir groups had longer hospital stays (P=0.002) and higher hospital expenses (P<0.001), compared with patients in the azvudine groups (Figure 5).

The Efficacy Evaluation of Nirmatrelvir/Ritonavir and Azvudine Combined Use for Antiviral

In clinical practice, we observed that a small number of patients received both nirmatrelvir/ritonavir and azvudine during the treatment of COVID-19. In order to evaluate the effect of nirmatrelvir/ritonavir and azvudine combined use, we collected the information of 41 patients who received nirmatrelvir/ritonavir and azvudine at the same time point. We found that the combination of nirmatrelvir/ritonavir and azvudine did not improve patient survival, length of stay, or hospital costs compared with using nirmatrelvir/ritonavir or azvudine alone (Figure 6).

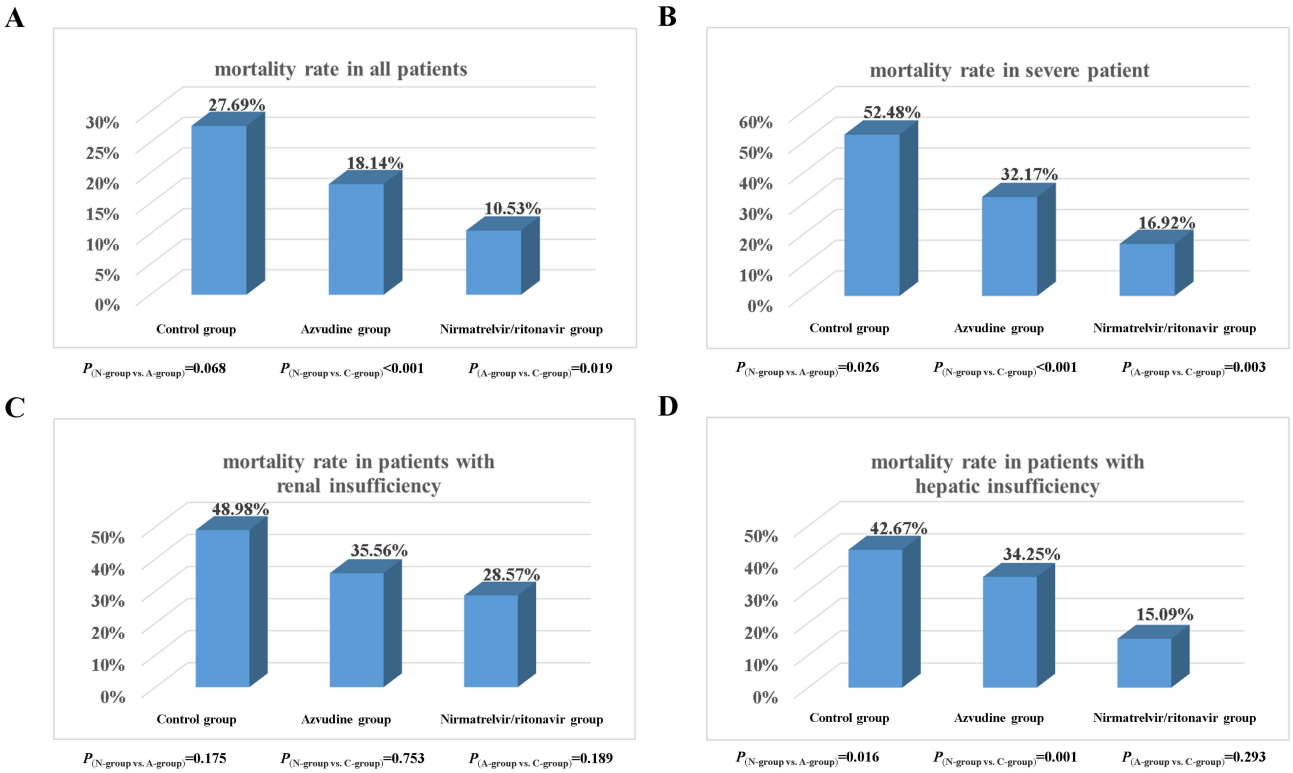

Figure 4 The mortality rates in the azvudine, nirmatrelvir/ritonavir, and control (no antiviral therapy) groups.
Notes: (**A**) Overall mortality by treatment group. (**B**) Mortality in patients with severe COVID-19 by treatment group. (**C**) Mortality in patients with renal insufficiency by treatment group. (**D**) Mortality in patients with hepatic insufficiency by treatment group. N-group: nirmatrelvir/ritonavir group; A-group: azvudine group; C-group: control group.

Discussion

When comparing the effectiveness of azvudine and nirmatrelvir/ritonavir in the treatment of COVID-19, it is crucial to control for the effect of confounding factors on the prognosis of the disease to ensure the validity of the results. In our study, we achieved a well-balanced distribution of confounding factors between groups. Age, sex, COVID-19 vaccination status, severity on admission, and treatment all influence the prognosis of COVID-19.[15–17] Therefore, these factors were considered potential confounding factors in our study. Furthermore, comorbidities, such as hypertension, diabetes, coronary heart disease, hepatitis, chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD) are all factors associated with poor prognosis in COVID-19.[18–24] Systemic steroids play an important role in the treatment of patients with COVID-19, particularly in those with severe COVID-19 pneumonia, as they help prevent disease complications and improve clinical outcomes.[25] Empiric antibiotic use in patients with COVID-19 does not prevent disease progression, reduce mortality, or shorten hospital stays;[26,27] however, the use of antibiotics may be necessary for patients with bacterial infections. It is currently unclear whether antibiotic treatment improves symptoms in patients with bacterial infections. Given that these factors can potentially influence the effectiveness of antiviral drugs in patients with COVID-19, we performed a detailed comparison of these indicators to check the balance of confounding factors between the azvudine and nirmatrelvir/ritonavir treatment groups. Additionally, we conducted a comprehensive comparison of laboratory test results to assess their effect as confounding factors. C-reactive protein (CRP) serves as an early predictive biomarker for hypoxia in COVID-19,[28] and elevated CRP levels may indicate a higher susceptibility to shortness of breath. Several studies have shown a strong association between the white blood cell, lymphocyte, monocyte, and neutrophil counts on admission in patients with COVID-19, and mortality.[29,30] A single-centre prospective cohort study revealed that serum albumin and creatinine are predictive indicators of acute kidney injury in patients with COVID-19, which can impact patient prognosis.[31] We successfully controlled for the influence of these confounding factors on the outcomes by comparing the laboratory test results of the azvudine and nirmatrelvir/ritonavir groups.

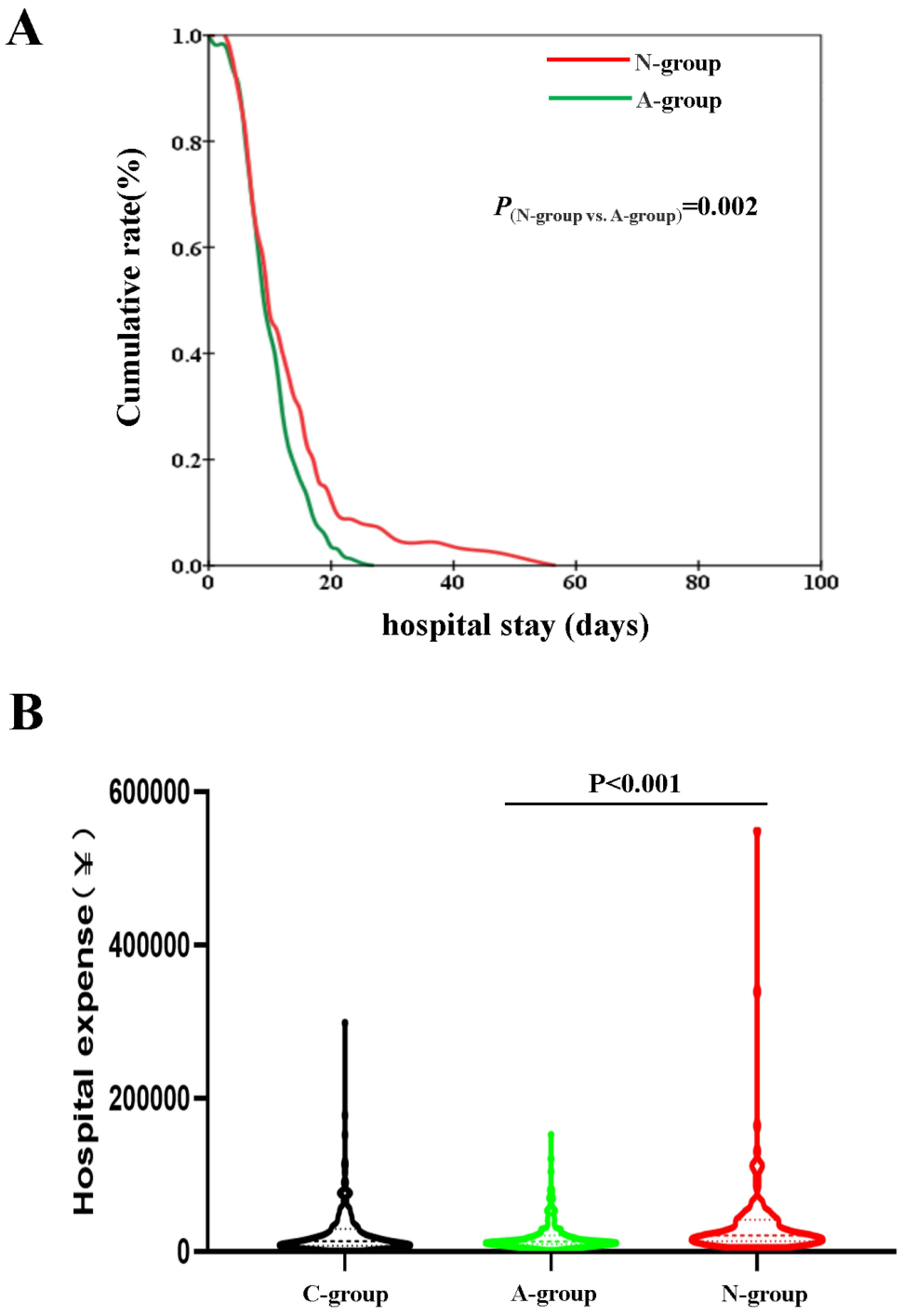

Figure 5 Length of hospital stay and cost of hospitalisation in the azvudine, nirmatrelvir/ritonavir, and control (no antiviral therapy) groups.
Notes: (**A**) Length of hospital stay by treatment group. (**B**) Hospitalisation cost by treatment group. N-group: nirmatrelvir/ritonavir group; A-group: azvudine group; C-group: control group.

Our findings revealed a similar incidence of symptoms between patients receiving azvudine and those receiving nirmatrelvir/ritonavir. However, patients treated with azvudine experienced a considerably shorter duration of weakness than those who received nirmatrelvir/ritonavir. Although there was no substantial difference in overall mortality between patients receiving azvudine and those receiving nirmatrelvir/ritonavir, in patients with severe disease, the mortality rate was substantially lower in patients treated with nirmatrelvir/ritonavir. Notably, among patients with renal insufficiency,

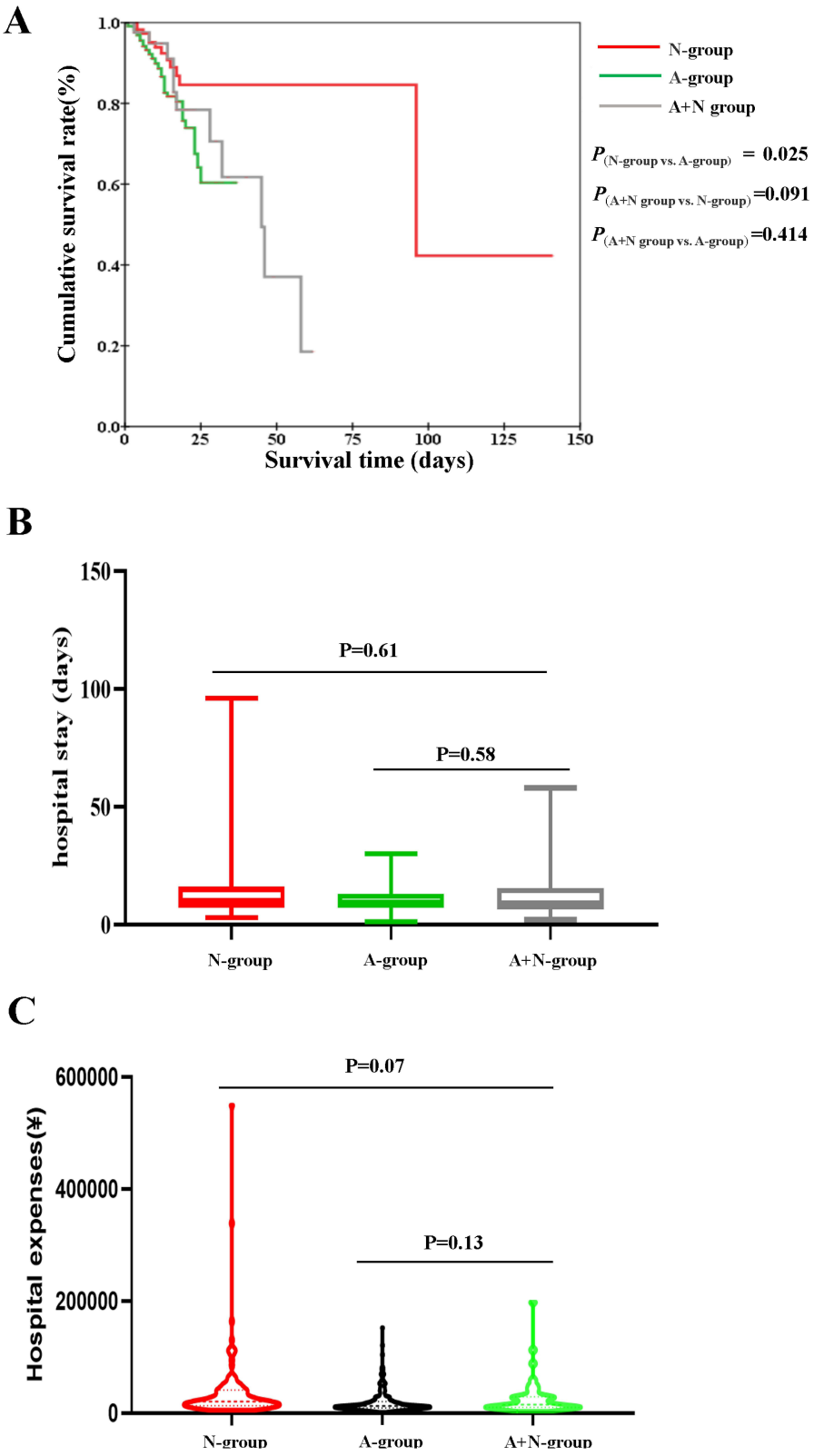

Figure 6 The survival rate, length of stay, and hospitalisation cost in patients with COVID-19 taking nirmatrelvir/ritonavir and azvudine concurrently.
Notes: (**A**) Survival rate by treatment group. (**B**) Length of stay by treatment group. (**C**) Hospitalisation cost by treatment group. A+N-group: Patients taking azvudine and nirmatrelvir/ritonavir concurrently; N-group: nirmatrelvir/ritonavir group; A-group: azvudine group.

no notable difference was observed in the effect of azvudine and nirmatrelvir/ritonavir on mortality. However, among patients with hepatic insufficiency, those receiving nirmatrelvir/ritonavir exhibited a considerably lower mortality rate than those who received azvudine. Ritonavir is a potent hepatic enzyme inhibitor; therefore, in patients with hepatic insufficiency, ritonavir might exert a stronger inhibitory effect on P450 CYP3A4, resulting in higher exposure to nirmatrelvir and lower mortality. In addition, we found that patients in the nirmatrelvir/ritonavir group had higher hospitalization costs. These higher hospitalization costs might be related to the patients' family economic conditions. In China, the price of a course of azvudine was about 170 RMB. Moreover, patients using azvudine can be reimbursed for part of the cost through medical insurance. However, the price of a course of nirmatrelvir/ritonavir was about 1700 RMB. Patients using nirmatrelvir/ritonavir tended to have a higher household income, and thus were more likely actively pursue better medical care, attention, and treatment, resulting in higher hospitalization costs.

To date, a limited number of studies have compared the effectiveness of azvudine and nirmatrelvir/ritonavir. Gao et al[11] conducted a study of 245 patients and used propensity-score matching to control for confounding factors. However, in our study, we achieved a balanced distribution of confounding factors at baseline upon enrolment, and the ratio of patients in the nirmatrelvir/ritonavir group to those in the azvudine group was nearly 2:1. Therefore, we did not employ propensity matching scores and ultimately included 576 patients. Dian et al[12] conducted a study involving 456 patients with COVID-19 receiving antiviral therapy and utilized propensity-score matching, but did not control for variables in the admission test results. Similar to Gao et al,[11] the confounding factors in the laboratory test results was balanced in our study to ensure the greatest possible reliability of the findings. Consistent with our study's results, studies by Zhao Q et al[32] and Zhao X et al[33] also found that there was no significant difference in overall mortality between the nirmatrelvir/ritonavir and azvudine groups. However, Dian et al[12] found that among patients with COVID-19 and comorbidities, the risk of composite disease progression was lower in the azvudine group than in the nirmatrelvir/ritonavir group.

Furthermore, we found that the combination therapy of the nirmatrelvir/ritonavir and azvudine did not improve patient survival, length of stay, or hospital costs compared with using nirmatrelvir/ritonavir or azvudine alone. Therefore, we do not recommend the concurrent use of nirmatrelvir/ritonavir and azvudine in patients with COVID-19.

Our study has several limitations. First, owing to the retrospective nature of the study, detailed data on vaccinations, such as the number and type of vaccines administered, were not fully recorded. Second, it was conducted at a single centre, and the sample size was relatively small. Therefore, further multicentre studies with larger sample sizes are necessary for validation. Third, there are numerous potential confounding factors that may affect the effectiveness of azvudine and nirmatrelvir/ritonavir, and residual confounding due to unmeasured confounders may be present. Fourth, SARS-CoV-2 mutations may change the effectiveness of antiviral therapy. Fifth, symptom data from patients with COVID-19 was recorded through patient self-report when the doctor was on the daily ward rounds. Patients' self-reports may be limited by their medical knowledge, resulting in recorded results that were not entirely consistent with actual conditions.

Conclusion

Our findings suggest that azvudine could be recommended for patients with non-severe COVID-19 and weakness, whereas nirmatrelvir/ritonavir could be recommended for patients with severe disease to reduce mortality, and it might be a better choice for patients with hepatic insufficiency. The concurrent use of nirmatrelvir/ritonavir and azvudine in patients with COVID-19 could be not generally recommended.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgments

We express our gratitude to the medical staff for their valuable involvement and support in this study.

Funding

This work was funded by the National Nature Science Foundation of China (Grant No. 81970038 and 8227004) and the Science and Technology Projects in Guangzhou, China (SL2022A04J00473).

Disclosure

The authors have no competing interests to declare that are relevant to the content of this article.

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