BMJ Open Respiratory Research

Effectiveness of nirmatrelvir-ritonavir versus azvudine for adult inpatients with severe or critical COVID-19

Huan Zhang ,[1,2] Tan Xiaojiao,[1] Junjun Chen,[1,3] Zheng Zhang,[1] Chenxi Wang,[1] Haiqing Shi,[1] Yao Li,[1] Jianbo Li,[1] Yan Kang,[1,3] Xiaodong Jin,[1] Xuelian Liao[1,3]

To cite: Zhang H, Xiaojiao T, Chen J, *et al*. Effectiveness of nirmatrelvir-ritonavir versus azvudine for adult inpatients with severe or critical COVID-19. *BMJ Open Respir Res* 2024;**11**:e001944. doi:10.1136/bmjresp-2023-001944

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjresp-2023-001944).

HZ and TX contributed equally.

Received 10 July 2023
Accepted 15 March 2024

[1]Department of Critical Care Medicine, West China Hospital of Sichuan University, Chengdu, People's Republic of China
[2]Department of Cardiac Vascular Surgery Critical Care Medicine, The Third People's Hospital of Chengdu, Chengdu, People's Republic of China
[3]Department of Critical Care Medicine, West China Tianfu Hospital of Sichuan University, Chengdu, People's Republic of China

Correspondence to
Professor Xuelian Liao; liaoxuelian@scu.edu.cn and

Mr Xiaodong Jin; zh_jxd@163.com

ABSTRACT

Background In China, both nirmatrelvir-ritonavir (Paxlovid) and azvudine have been granted approval to treat adult SARS-CoV-2-infected patients with moderate symptoms. Information about the clinical effect of the two available agents among inpatients with severe or critical COVID-19 is scarce.

Purpose To compare the clinical outcomes of Paxlovid and azvudine among adult inpatients with severe or critical COVID-19.

Method We conducted a retrospective cohort study in two large medical centres after the epidemic control measures were lifted in China. A new propensity score matched-inverse probability of treatment weighting cohort was constructed to evaluate the in-hospital all-cause mortality, hospital length of stay, Sequential Organ Failure Assessment (SOFA) score and safety.

Results A total of 955 individuals were in the cohort. The antiviral therapy strategies were decided by the senior physician and the supplies of the pharmacy. A total of 451 patients were in the Paxlovid group, and 504 patients were in the azvudine group. Compared with Paxlovid, the effects of azvudine on in-hospital all-cause mortality were not significantly different, and the OR (95% CI) was 1.084 (0.822 to 1.430), and the average hospital length of stay of patients discharged alive was also similar in the azvudine group, and the difference (day) and (95% CI) was 0.530 (−0.334 to 1.393). After 7 days of therapy, the degree of decline in the SOFA score was greater in the Paxlovid group than in the azvudine group (p<0.001). The change in glomerular filtration rate was not significantly different (p=0.824).

Conclusion Paxlovid and azvudine had similar effectiveness on in-hospital all-cause mortality and hospital length of stay. Compared with the azvudine group, after 7 days of therapy, the degree of decline in SOFA score was significantly higher in the Paxlovid group. These findings need to be verified in larger prospective studies or randomised controlled trials.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Both Paxlovid and azvudine can shorten the SARS-CoV-2 nucleic acid negativity time and be clinically effective in mild-to-moderate patients. An evaluation of the clinical efficacy of antiviral therapy in severe or critical COVID-19 inpatients is urgent but lacking.

WHAT THIS STUDY ADDS

⇒ By using an inverse probability of treatment weighting and propensity score matched cohort, our study provides an important therapeutic reference for severe or critical COVID-19 inpatients. Paxlovid and azvudine have similar effectiveness on in-hospital all-cause mortality and hospital length of stay in adult inpatients with severe or critical COVID-19. Compared with the azvudine group, after 7 days of therapy, the degree of decline in Sequential Organ Failure Assessment score was significantly higher in the Paxlovid group.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results force us to rethink the selection and prioritisation of antiviral agents for adult inpatients with severe or critical COVID-19. This study will also help and motivate the researchers to extend the preclinical and clinical research on antivirals.

INTRODUCTION

The worldwide COVID-19 pandemic, caused by SARS-CoV-2, has greatly threatened human health.[1] Even now, 37 650 patients are still in serious or critical condition worldwide,[2] which highlights the importance of research on therapeutic drugs.

In China, the whole COVID-19 vaccination rate is 91.9%,[3] which helps relieve the incidence of critical illness.[4] Also, in our study, the three doses of COVID-19 vaccination rate was 91.4% and 94.2% in the Paxlovid group and in the azvudine group, respectively, which is shown in table 1. After the control measures for the SARS-CoV-2 epidemic were lifted at the end of 2022, asymptomatic, mild and self-limiting symptoms were the main clinical manifestations of COVID-19 infection. The patients who needed to be hospitalised were often in severe or critical condition, including respiratory insufficiency, multiple organ dysfunction, shock and even death.[5]

The Chinese administration authorised the use of Paxlovid and azvudine for mild

Table 1 Demographic and clinical characteristics of the 955 eligible patients

Characteristic	Azvudine group (N=504)	Paxlovid group (N=451)	P value
Age (mean±SD) - years	68.67±15.07	68.81±17.40	0.897
Male (N, (%))	341 (67.7)	314 (69.6)	0.514
Non-vaccination (N, (%))	20 (4.0)	29 (6.4)	0.085
Primary vaccination (N, (%))	503 (99.8)	447 (99.1)	0.141
Two doses vaccination (N, (%))	496 (98.4)	445 (98.7)	0.742
Three doses vaccination (N, (%))	475 (94.2)	412 (91.4)	0.083
Duration since symptom onset Median (range) - days	8 (5–13)	9 (6–13)	0.126
Comorbidities (N, (%))			
Heart dysfunction	111 (22.0)	118 (26.2)	0.032
Pulmonary dysfunction	165 (32.7)	165 (36.6)	0.212
Liver dysfunction	82 (16.3)	78 (17.3)	0.672
Kidney dysfunction	64 (12.7)	70 (15.5)	0.210
Malignancy	69 (13.7)	65 (14.4)	0.748
Immunocompromised status	136 (27.0)	147 (32.6)	0.058
Aetiology (N, (%))			
Bacteria	84 (16.7)	81 (18.0)	0.598
Candida	143 (28.4)	126 (27.9)	0.881
Treatment (N, (%))			
Tocilizumab	21 (4.2)	30 (6.7)	0.088
Baricitinib	20 (2.1)	20 (4.4)	0.719
Antibiotic	474 (94.0)	418 (92.7)	0.396
Steroids	339 (67.3)	364 (80.7)	<0.001
Immunoglobulins	97 (21.5)	73 (14.5)	0.006
SOFA score on Day 1 (mean±SD)	3.49±1.78	3.19±1.76	0.007

N, number; SOFA, Sequential Organ Failure Assessment.

to moderate COVID-19-infected patients in 2022.[6 7] As the antiviral therapy for inpatients with severe or critical SARS-CoV-2 is urgent, researchers have paid great attention to therapeutic strategies for inpatients with severe or critical conditions. Due to the limitations of antiviral drugs, both Paxlovid and azvudine were extensively used to quell the surge of the Omicron variant. However, information on the therapeutic effect of these two drugs for inpatients with severe or critical SARS-CoV-2 is scarce. More studies are needed to explore the suitability of Paxlovid and azvudine. In this retrospective cohort study, we compared the clinical effects of Paxlovid and azvudine among inpatients with severe or critical SARS-CoV-2.

MATERIALS AND METHODS

Patient and public involvement

Both patients and the public were not involved in the study design or conduct, also were not involved with the reporting or dissemination plans of the research.

Study design and data source

All the protocols of our study conformed to the Declaration of Helsinki. In this retrospective study, all the patients signed informed consent forms to authorise the use of their anonymised clinical data for future scientific research purposes on admission. Therefore, additional informed consent for this study was waived. All patient data were retrieved from the medical record database. Before the analysis, all data involved in this study were anonymised by the information department.

We built a new propensity score matched-inverse probability of treatment weighting (IPTW) cohort study at two large referral centres in Western China for patients, West China Hospital and West China Tianfu Hospital. SARS-CoV-2 infection was diagnosed by a positive reverse-transcription PCR assay. A total of 6695 inpatients were enrolled by using medical records from 7 December 2022 to 1 February 2023. The antiviral therapy strategies were decided by the senior physician and were also

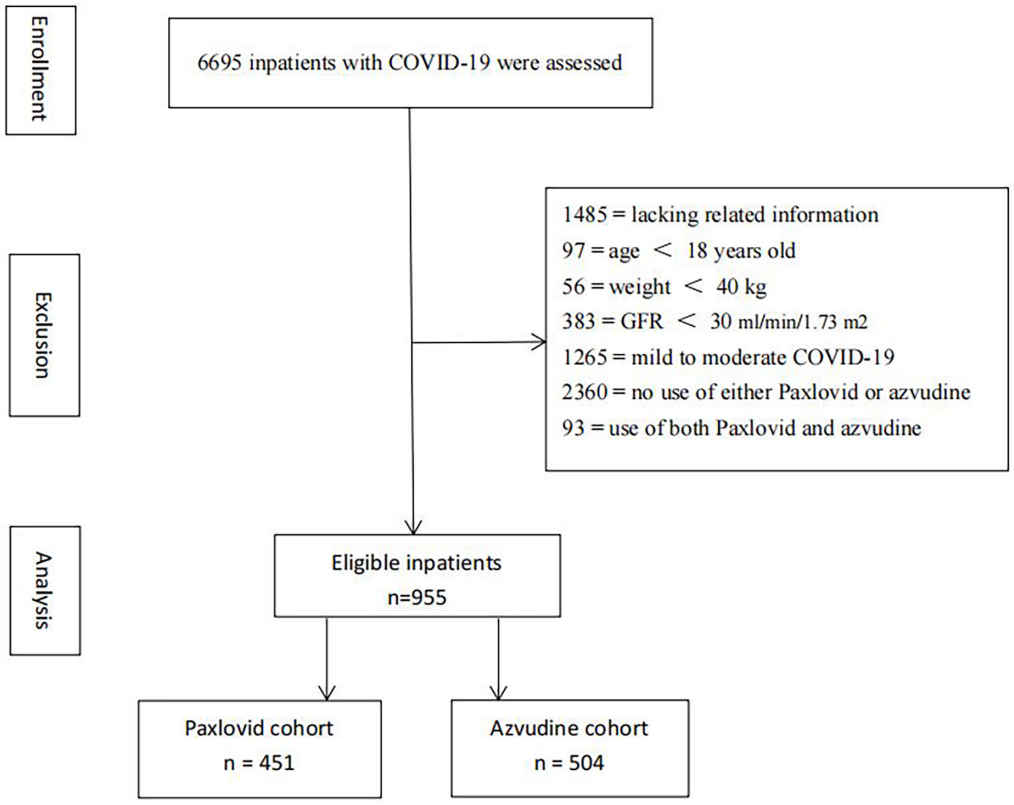

Figure 1 Flowchart of inpatient inclusion. GFR, glomerular filtration rate.

affected by the two antiviral drugs supplied by the pharmacy. Only one antiviral drug was available in many cases, as Paxlovid and azvudine were urgently needed during the pandemic.

The inclusion criteria were as follows: (1) adults with a weight greater than or equal to 40 kg; (2) adults with a positive SARS-CoV-2 test result at admission; and (3) adults in serious or critical clinical condition; and (4) adults who received either Paxlovid or azvudine.

In China, the diagnosis of serious or critical infection with SARS-CoV-2 is made according to the criteria of the 10th trial edition of the Guidelines on the Diagnosis and Treatment of COVID-19 in China, including (1) panting with a breathing rate ≥30 breaths/min; (2) SpO2≥93% when inhaling air at rest; (3) PaO2 divided by FiO2≥300 mm Hg; (4) progressively worsening clinical manifestations and significant progression of an internal lesion on pulmonary radiography >50% within 24–48 hours; (5) mechanical ventilation dependence; (6) shock; and (7) organ failure requiring intensive care.[8]

The exclusion criteria were as follows: (1) missing information on the treatment or discharge diagnosis; (2) renal failure with dialysis or a glomerular filtration rate (GFR)<30 mL/min/1.73 m^2 within the past 6 months; (3) contraindication or allergy to the components of the two drugs (Paxlovid or azvudine); (4) no use of either Paxlovid or azvudine; (5) use of both Paxlovid and azvudine; and (6) HIV infection.

The discharge criteria were dependent on the criteria of the 10th trial edition of the Guidelines on the Diagnosis and Treatment of COVID-19 in China: (1) all clinical conditions improved significantly; (2) the vital signs were stable, and the patient remained afebrile for more than 24 hours; (3) the acute exudative lesions had improved significantly on the lung imaging; (4) the patient depended mildly on oral drugs; and (5) no complications required further management.[8]

Demographic characteristics, comorbidities identified by diagnosis codes, related therapies, clinical results, Sequential Organ Failure Assessment (SOFA) scores and other related clinical and laboratory examinations were collected. We defined Day 1 as the day of initiation of antiviral therapy. Related clinical and laboratory tests were performed within the next 7 days. All the above parameters were obtained from the worst results for each day.

Cohort definition

After hospitalisation, in the Paxlovid group, Paxlovid was prescribed as 300 mg of nirmatrelvir and 100 mg of ritonavir or 150 mg of nirmatrelvir plus 50 mg of ritonavir if the patient's GFR was within the range from 45 to 30 mL/min/1.73 m^2 every 12 hours for 5 days. In the azvudine group, patients were treated with azvudine once daily at night. In addition, all patients in both groups received standard treatment based on the Guidelines on the Diagnosis and Treatment of COVID-19 (10th trial edition).[8]

Table 2 Multivariable analysis of all-cause mortality for 955 patients after using an inverse probability of treatment-weighted cohort based on propensity scores

	IPTW cohort		Original cohort	
Item	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)
Paxlovid vs azvudine	0.567	1.084 (0.822 to 1.430)	0.625	1.102 (0.746 to 1.634)
Age	<0.001	1.029 (1.018 to 1.041)	<0.001	1.029 (1.013 to 1.045)
Course	0.396	0.988 (0.959 to 1.016)	0.459	0.985 (0.945 to 1.025)
One dose of vaccination	0.596	1.806 (0.122 to 13.161)	0.746	1.511 (0.065 to 15.385)
Two doses of vaccination	0.760	1.246 (0.269 to 4.692)	0.975	0.968 (0.095 to 6.024)
Three doses of vaccination	0.634	1.156 (0.651 to 2.160)	0.916	0.957 (0.439 to 2.273)
Immunocompromised status	0.366	0.857 (0.611 to 1.194)	0.348	0.797 (0.491 to 1.271)
Steroids	<0.001	2.119 (1.409 to 3.280)	0.034	1.838 (0.067 to 3.315)
Tocilizumab	<0.001	2.933 (1.816 to 4.725)	0.002	2.999 (1.506 to 5.954)
Baricitinib	0.634	1.155 (0.626 to 2.055)	0.758	1.143 (0.468 to 2.591)
Immunoglobulins	<0.001	2.572 (1.847 to 3.574)	<0.001	2.768 (1.739 to 4.393)
Bacteria	0.003	1.683 (1.187 to 2.370)	0.056	1.606 (0.980 to 2.591)
Candida	<0.001	1.737 (1.293 to 2.333)	0.008	1.752 (1.156 to 2.648)
SOFA score on Day 1	<0.001	1.451 (1.344 to 1.568)	<0.001	1.444 (1.298 to 1.612)

SOFA, Sequential Organ Failure Assessment.

Outcomes

The primary outcome was in-hospital all-cause mortality. The secondary outcomes were the length of hospital stay, the improvement in multiorgan dysfunction reflected by the SOFA score and the ratio of patients with an improvement in the SOFA score ≥2 on Day 7. Other related clinical laboratory tests were also analysed on Day 7. Further exploratory subgroup analyses were performed based on the course of the disease.

Statistical analysis

In the study cohort, if the quantitative data conformed to a normal distribution, we used the means and SD to present the data distribution. If not, we used the medians and IQRs. The qualitative data were presented as the number of patients and proportions.

IPTW incorporating propensity scores was used to modulate the differences between the two groups. A non-significant difference occurs when the p value is equal to

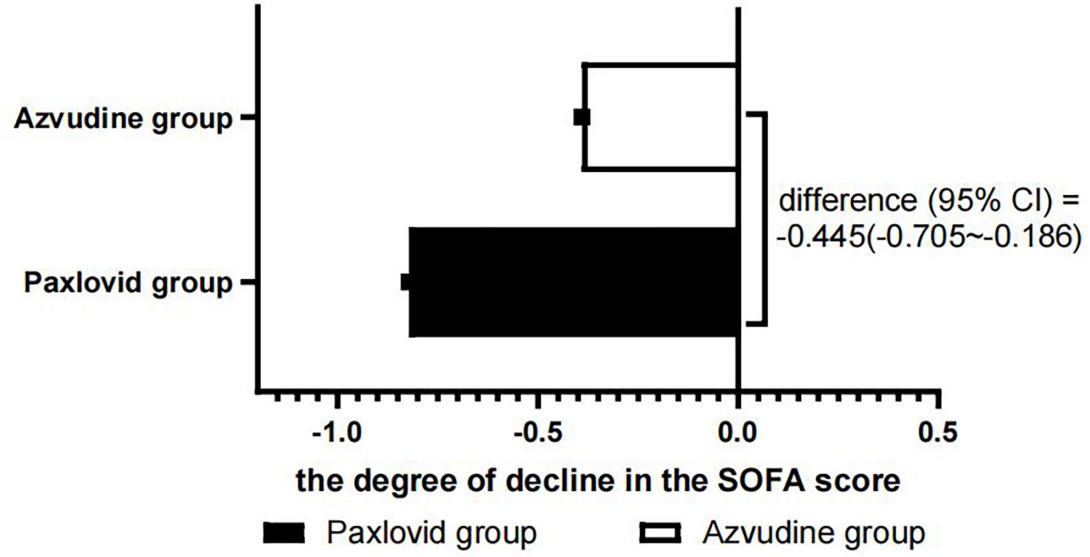

Figure 2 The degree of decline in SOFA score from day 7 to day 1 between the two groups. After 7 days of therapy, the degree of decline in the SOFA score in the Paxlovid and azvudine group was –0.822±2.074 and –0.390±2.002, respectively. The lower degree in SOFA score (day 7 vs day 1) was significantly higher in the Paxlovid group, the difference (95% CI) = –0.445 (–0.705 to –0.186). SOFA, Sequential Organ Failure Assessment.

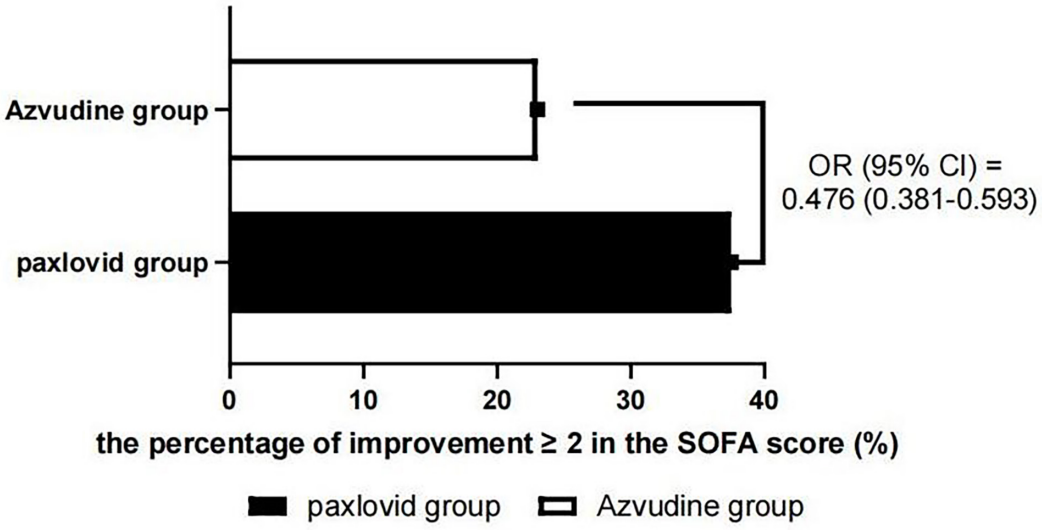

Figure 3 The difference of the ratio of improvement ≥2 in the SOFA score between two groups. The ratio of patients with an SOFA score improvement ≥2 in the Paxlovid group was higher than that in the azvudine group (37.5% vs 23.0%) and the OR (95% CI) was 0.476 (0.381 to 0.593). SOFA, Sequential Organ Failure Assessment

or greater than 0.05 for the baseline covariate. Multivariable statistical methods were used to assess the relationships after adjusting for bias and confounders.

The bias and confounders related to the therapeutic strategies and the results were used in generating the propensity score on the initial day of antiviral therapy and included age, disease course, SOFA score on the day of the initial antiviral treatment, immunocompromised status and pneumonia, tocilizumab, baricitinib, steroid, immunoglobulin and antibiotic use and coinfection with bacteria or *Candida*. We chose IPTW to adjust for confounders, as it allowed almost all eligible patients to be included in the analysis. The differences in baseline information were analysed by Pearson's χ^2 test for categorical variables or the independent-samples t-test for continuous variables. In the IPTW weighting cohort, ORs and 95% CIs for the primary outcome were estimated using weighted regression.

R V.4.3.0 was used for statistical analysis. A p<0.05 (two-sided) was considered statistically significant.

RESULTS

Patients

A total of 6695 inpatients infected with the SARS-CoV-2 Omicron variant were selected from the medical records

Table 3 Subgroup analysis of all-cause mortality according to disease course

	Early antiviral subgroup		Late antiviral subgroup	
Item	**P value**	**Adjusted OR (95% CI)**	**P value**	**Adjusted OR (95% CI)**
Paxlovid vs azvudine	0.619	1.179 (0.613 to 2.265)	0.647	1.076 (0.785 to 1.476)
Age	0.010	1.034 (1.008 to 1.063)	<0.001	1.027 (1.014 to 1.040)
Course	0.402	0.873 (0.633 to 1.200)	0.473	1.014 (0.976 to 1.052)
One dose of vaccination	0.990	0.000 (–)	0.352	3.155 (0.187 to 32.985)
Two doses of vaccination	0.400	0.182 (0.000 to 7.194)	0.586	1.589 (0.215 to 7.117)
Three doses of vaccination	0.939	0.927 (0.155 to 8.668)	0.478	1.258 (0.685 to 2.451)
Immunocompromised status	0.006	0.308 (0.128 to 0.686)	0.782	1.056 (0.717 to 1.544)
Steroids	0.307	1.515 (0.695 to 3.452)	<0.001	2.914 (1.718 to 5.275)
Tocilizumab	<0.001	7.201 (2.512 to 22.161)	0.011	2.038 (1.649 to 3.473)
Baricitinib	0.576	1.532 (0.298 to 6.300)	0.712	1.131 (0.575 to 2.137)
Immunoglobulins	0.002	3.827 (1.656 to 8.887)	<0.001	2.396 (0.717 to 1.544)
Bacteria	0.211	0.543 (0.195 to 1.344)	<0.001	2.244 (1.523 to 3.291)
Candida	0.402	0.726 (0.350 to 1.462)	<0.001	2.323 (1.656 to 3.265)
SOFA score on Day 1	<0.001	1.855 (1.514 to 2.312)	<0.001	1.397 (1.284 to 1.522)

SOFA, Sequential Organ Failure Assessment;

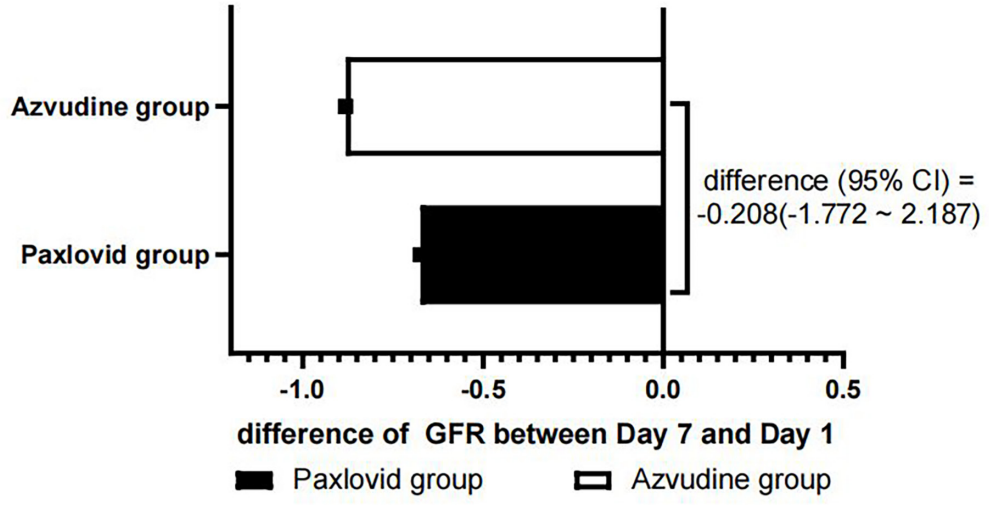

Figure 4 Degree of change of GFR (day 7 vs day 1) between the two group. After 7 days of therapy, the degree of change in the GFR in the Paxlovid and azvudine group was −0.674±15.695 and −0.881±15.096, respectively. The degree of change in GFR after 7 days of the two groups was not significantly different, difference (95% CI) = −0.208 (−1.772 to 2.187). GFR, glomerular filtration rate.

at West China Hospital and West China Tianfu Hospital from 7 December 2022 to 1 February 2023. A total of 955 patients who met the inclusion criteria for severe or critical COVID-19 were finally analysed. A total of 451 patients received Paxlovid therapy plus standard treatment, and 504 patients were in the azvudine group (figure 1 flowchart of inpatient inclusion).

Baseline characteristics

The baseline characteristics at admission according to the two different groups are displayed in table 1. The mean (±SD) age of all included patients was 68.74 (±16.20) years, and the number of women was 300 (31.4%). The median course of the disease before hospital admission was 8 days. Compared with the azvudine cohort, the SOFA score on Day 1 of the Paxlovid plus standard treatment patients was much lower (3.49±1.78 vs 3.19±1.76, p=0.007). Additionally, some specific therapeutic strategies for COVID-19 were imbalanced between the two groups. Fewer patients received steroids in the azvudine group (p<0.001). The baseline characteristics were imbalanced between the two groups, which may have affected the choice of therapeutic strategies or clinical results. In the new IPTW cohort, there were negative differences in related covariates between the two groups, which are displayed in online supplemental table 1.

Primary outcome

There were 78 (17.3%) in-hospital all-cause deaths in the azvudine group and 76/504 (15.1%) in the Paxlovid group. Additionally, after eliminating heterogeneous covariates, Compared with the Paxlovid group, the rate of in-hospital all-cause mortality of the azvudine group was not significantly different by adjusted regression analyses in the new IPTW cohort, and the OR (95% CI) was 1.084 (0.822 to 1.430), as shown in table 2.

In this study, the SOFA score, which reflected the severity of the clinical condition on the first day of antiviral treatment, was an independent risk factor for increased odds of all-cause mortality in the hospital and the OR (95% CI) was 1.451 (1.344 to 1.568). Other factors included age, with an OR (95% CI) of 1.029 (1.018 to 1.041), and specific therapeutic strategies, such as steroid therapy, with an OR (95% CI) of 2.119 (1.409 to 3.280). Coinfection with bacteria or *Candida* aggravated in-hospital all-cause mortality, with ORs (95% CI) of 1.683 (1.187 to 2.370) and 1.737 (1.293 to 2.333), respectively.

Secondary outcome

There was no significant difference in the length of hospital stay among patients who were discharged alive between the Paxlovid group and the azvudine group, which were 15.072±6.399 days and 15.063±7.032 days, respectively (p=0.985). In the IPTW cohort, after multiple sensitivity analyses, initiation of Paxlovid or azvudine had a similar effect on the length of stay and the difference (day) and 95% CI was 0.530 (−0.334 to 1.393).

After 7 days of therapy, the degree of decline in the SOFA score was greater in the Paxlovid group, as shown in figure 2. The total number of patients with an improvement in the SOFA score ≥2 was 285 (29.8%). The ratio of patients with an SOFA score improvement ≥2 in the Paxlovid group was higher than that in the azvudine group (37.5% vs 23.0%). Additionally, in the new IPTW group, Paxlovid was superior to azvudine therapy and the OR (95% CI) was 0.476 (0.381 to 0.593), as shown in figure 3.

Subgroup analysis

According to the course of symptom onset since admission, inpatients whose course was less than 5 days were

included in the early antiviral group, and vice versa. Other inpatients were classified as the late antiviral group. In the new IPTW group, the rate of in-hospital all-cause mortality was similar in the early and late antiviral subgroups, as shown in table 3. Additionally, the length of stay was not distinctive in the early and late antiviral groups among patients who were discharged alive, and the differences in days and 95% CI were 1.082 (−0.799 to 2.963) and 0.308 (−0.677 to 1.294), respectively.

Safety outcome

There was no significant difference in the GFR on Day 1 between the Paxlovid group and the azvudine group (72.52±23.86 vs 76.29±21.60). Additionally, in the new IPTW group, after 7 days of therapy, the mean GFR of the two groups was similar (p=0.279). Additionally, the degree of change in the GFR after 7 days of treatment was not significantly different (p=0.824), as shown in figure 4.

DISCUSSION

Both Paxlovid and azvudine can shorten the SARS-CoV-2 nucleic acid negativity time and are clinically effective among mild-to-moderate patients.[9 10] The evaluation of the clinical efficacy of antiviral therapy in severe or critical COVID-19 inpatients is urgent but limited. In this multicentre retrospective cohort study, a total of 6695 inpatients were enrolled. Finally, 955 severe to critical COVID-19 inpatients were included. A total of 451 inpatients were prescribed Paxlovid, and 501 inpatients received azvudine. After constructing a new IPTW cohort, our data indicated that Paxlovid and azvudine had similar effects on clinical outcomes, including in-hospital all-cause mortality and length of stay. After 7 days of therapy, in the Paxlovid group, the patients experienced lower SOFA scores and the ratio of an SOFA score improvement ≥2 was higher than that in the azvudine group. In the analysis of the change in GFR that reflected the nephrotoxicity of the two drugs, there was also no notable difference between the two groups.

A real-world study conducted in Beijing, China, showed that patients who received Paxlovid experienced faster viral clearance than patients who received azvudine.[11] The severity of the disease may be influenced by the viral load.[12] However, they did not explore the clinical outcomes between the two drugs. In our real-world clinical study, no significant differences were observed in all-cause mortality in the hospital between the two antiviral drugs against SARS-CoV-2. We used the SOFA score to reflect systemic organ function and found that patients prescribed Paxlovid had lower SOFA scores and that the ratio of improvement ≥2 in the SOFA score was higher on Day 7.

Our study findings were different from those of another study conducted from 5 December 2022 to 31 January 2023, in China.[13] That study did not include inpatients who needed oxygen support or mechanical ventilation on admission. However, approximately 64% suffered severe conditions. All of these severe inpatients may have needed oxygen support, which may have confounded the clinical results. As Guangting Zeng assessed, other biases may have interfered with the reliability of the conclusions.[14]

Paxlovid has been authorised for the treatment of mild-to-moderate COVID-19 within 5 days of symptom onset.[15 16] In our research, the percentage of patients whose course was within 5 days since symptom onset was only 20.21%. Therefore, a subgroup analysis was conducted according to the time since symptom onset, and the cut-off value was 5 days. However, in both subgroups, no significant difference was found in the risk of all-cause mortality in the hospitals.

There were some limitations in this study. First, we did not include every factor as a covariate, which had a slight effect on the selection of two drugs and all-cause mortality. Second, as this was a retrospective study, we did not explore 28-day or 90-day mortality between the two groups, which may have led to serious bias. Moreover, we did not evaluate the viral load after the initiation of the antiviral therapy. Finally, safety data on these two drugs were limited. Therefore, the results of our main outcomes may have a risk of being underpowered.

CONCLUSION

Paxlovid and azvudine had similar effectiveness on in-hospital all-cause mortality and length of hospital stay in severe or critical inpatients with COVID-19. Compared with the azvudine group, after 7 days of therapy, the SOFA score had a greater degree of decline in the Paxlovid group. It should be noted that the findings in this study need to be verified in larger prospective studies or randomised controlled trials.

Acknowledgements All authors gave thanks to the West China Hospital, Sichuan University and West China Tianfu Hospital for data supply that made the study possible. The authors extend gratitude to all data collectors for their cooperation and efforts during the data collection.

Contributors HZ and TX: Conceptualisation, Methodology, Software, Data curation, Formal analysis, Writing—Original draft preparation. JC, ZZ, CW, HS and YL: Investigation, Resources, Visualisation. JL: Software, Validation. YK, XJ, XL: Supervision, Writing—Reviewing and Editing. Guarantor: XL.

Funding This work was supported by the National key research and development plan of China (grant number 2022YFC2009804) and Key Research and Development Project of Science and Technology Department of Sichuan Province (grant number 2021YFS0003).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The local Ethical Committee of West China Hospital approved this study (Approval No. 2023-30). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iD

Huan Zhang http://orcid.org/0000-0002-9077-9331

REFERENCES

1 Tay MZ, Poh CM, Rénia L, *et al*. The Trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020;20:363–74.
2 COVID - Coronavirus Statistics - Worldometer. Available: worldometers.info [Accessed 9 Jun 2023].
3 Wu Y, Liu J, Liu M, *et al*. Progress in global COVID-19 vaccine development and vaccination strategies. *Chin J Dis Control Prev* 2023;27.
4 McMenamin ME, Nealon J, Lin Y, *et al*. Vaccine effectiveness of one, two, and three doses of BNT162b2 and Corona Vac against COVID-19 in Hong Kong: a population-based observational study. *The Lancet Infectious Diseases* 2022;22:1435–43.
5 Iype E, Gulati S. Understanding the asymmetric spread and case fatality rate (CFR) for COVID-19 among countries. *Infectious Diseases (except HIV/AIDS)* [Preprint] 2020.
6 National Medical Products Administration. China grants conditional approval for Pfizer's oral COVID-19 drug, 2022. Available: http://english.nmpa.gov.cn/2022-02/14/c_707085.htm [Accessed 10 Mar 2023].
7 National Medical Products Administration. Domestically developed drug joins virus battle, 2022. Available: http://english.nmpa.gov.cn/2022-08/15/c_797867.htm [Accessed 10 Mar 2023].
8 Notice on issuing the diagnosis and treatment plan for novel Coronavirus infection (trial version 10). n.d. Available: https://www.gov.cn/zhengce/zhengceku/2023-01/06/content_5735343.htm
9 Zheng Q, Ma P, Wang M, *et al*. Efficacy and safety of Paxlovid for COVID-19: a meta-analysis. *J Infect* 2023;86:66–117.
10 Ren Z, Luo H, Yu Z, *et al*. A randomized, open-label, controlled clinical trial of Azvudine tablets in the treatment of mild and common COVID-19, a pilot study. *Adv Sci (Weinh)* 2020;7:2001435.
11 Gao Y, Luo Z, Ren S, *et al*. Antiviral effect of Azvudine and Nirmatrelvir-Ritonavir among hospitalized patients with COVID-19. *J Infect* 2023;86:e158–60.
12 Zheng S, Fan J, Yu F, *et al*. Yu F, et al viral load Dynamics and disease severity in patients infected with SARS-Cov-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. *BMJ* 2020;369:m1443.
13 Deng G, Li D, Sun Y, *et al*. Real-world effectiveness of Azvudine versus Nirmatrelvir-Ritonavir in hospitalized patients with COVID-19: A retrospective cohort study. *J Med Virol* 2023;95:e28756.
14 Zeng G, Wang L, Li J, *et al*. Real-world effectiveness of Azvudine versus Nirmatrelvir-Ritonavir in hospitalized patients with COVID-19. *Journal of Medical Virology* 2023;95.
15 Hammond J, Leister-Tebbe H, Gardner A, *et al*. Oral Nirmatrelvir for high-risk, Nonhospitalized adults with COVID-19. *N Engl J Med* 2022;386:1397–408.
16 Dal-Ré R, Becker SL, Bottieau E, *et al*. Availability of oral Antivirals against Sars8 Cov-2 infection and the requirement for an ethical prescribing approach. *Lancet Infect Dis* 2022;22:e231–8.