Antiviral effectiveness and survival correlation of azvudine and nirmatrelvir/ritonavir in elderly severe patients with COVID-19: a retrospective real-world study

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Summary

Background Azvudine and nirmatrelvir/ritonavir are approved to treat mild-to-moderate coronavirus disease 2019 (COVID-19) in adults with a high risk for progression to severe infection. We sought to compare the antiviral effectiveness and clinical outcomes of elderly severe patients with COVID-19 receiving these two antiviral agents.

Methods In this observational study, we identified 249 elderly patients with severe COVID-19 infection who were admitted to the Second Medical Center of the People's Liberation Army General Hospital from December 2022 to January 2023, including 128 azvudine recipients, 66 nirmatrelvir/ritonavir recipients and 55 patients not received antiviral treatments. We compared the cycle threshold (Ct) value dynamic change of all three groups. The primary outcome was a composite outcome of disease progression, including all-cause death, intensive care unit admission, and initiation of invasive mechanical ventilation. The outcomes of all enrolled patients were followed up from the electronic medical record system. Kaplan–Meier and Cox risk proportional regression analyses were used to compare the clinical outcomes of all three groups. To more directly compare the effectiveness of the two antiviral drugs, we performed propensity-score matching between the two antiviral groups and compared antiviral efficacy and clinical outcomes in the matched population.

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Findings Among 249 patients (mean age, 91.41 years), 77 patients died during the follow-up period. When compared to patients who did not receive any antivirals, neither nirmatrelvir/ritonavir nor azvudine demonstrated a survival benefit. The Cox analysis of the all-cause death of the three groups showed that the risk of death was 0.730 (0.423–1.262) in the azvudine group 0.802 (0.435–1.480) and in the nirmatrelvir/ritonavir group compared with the non-antiviral group. After propensity score matching, we included 58 azvudine recipients and 58 nirmatrelvir/ritonavir recipients. The fitted curve of the Ct value after matching illustrated that the rate of viral decline in the early stage of nirmatrelvir/ritonavir treatment seems to surpass that of azvudine, but there was no statistical significance. Azvudine was seemly associated with a lower risk of composite outcomes (HR:1.676, 95% CI:0.805–3.488) and short-term all-cause death (HR: 1.291, 95%CI: 0.546–3.051).

Interpretation Patients who received azvudine have a similar antiviral effectiveness and survival curve trend compared to nirmatrelvir/ritonavir. In this limited series, antiviral treatment was not associated with a significant clinical benefit. This lack of clinical benefit might be attributed to potential bias.

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Keywords: COVID-19; Elderly; Azvudine; Nirmatrelvir/ritonavir

Research in context

Evidence before this study

We searched PubMed and MedLine to identify primary studies on the effectiveness of the two antiviral drugs for patients with COVID-19. The search strategy contained three modules: antiviral drugs, azvudine, and nirmatrelvir/ritonavir, COVID-19, and a filter of publication time till 30th September 2023. Studies were included if they involved a comparative study of azvudine and nirmatrelvir/ritonavir or an analysis of the efficacy of COVID-19 drugs in the elderly. Studies compare the efficacy and safety of azvudine and nirmatrelvir/ritonavir in treating COVID-19 infection, but the results are inconsistent. Moreover, most studies did not take age into account. There is an urgent need to explore the applicability of the previous findings in elderly severe patients to assist in clinical decision-making.

Added value of this study

This study included 194 elderly patients with severe COVID-19, with an average age of 91.41 years. It compared the antiviral effectiveness and short-term mortality and complications among elderly patients with severe COVID-19 infection who received nirmatrelvir/ritonavir or azvudine. The result showed that azvudine showed a similar antiviral effectiveness and survival outcomes with nirmatrelvir/ritonavir in super elderly patients with severe COVID-19 infection.

Implications of all the available evidence

This study shows real-world differences between oral antivirals in antiviral effectiveness and clinical outcomes, consisting primarily of super-elderly patients with COVID-19 infection. These data extend the evidence from clinical trials of those super-elderly patients with severe COVID-19 infection, and we hope that these data could provide a reference for the selection and prioritization of antiviral drugs in these populations.

Introduction

In December 2022, China experienced the first wave of mass COVID-19 infection caused by genomic subvariants BF.7 and BA.5.2. Azvudine and nirmatrelvir/ritonavir are the main antiviral drugs used in China.[1,2] Previous studies have shown the effectiveness of azvudine or nirmatrelvir/ritonavir in patients with COVID-19.[3–6] Hammond et al. found that nirmatrelvir/ritonavir reduced hospitalization and death by 89% in symptomatic, unvaccinated, non-hospitalized adults at high risk for progression to severe COVID-19 when started within three days of symptom onset, and results were similar in people starting nirmatrelvir/ritonavir within five days of symptom onset.[7] In addition, azvudine was associated with a significantly lower risk of composite disease progression outcomes compared with controls, especially in males and patients with severe COVID-19.[8]

Several studies compare the efficacy and safety of azvudine and nirmatrelvir/ritonavir in treating COVID-19 infection, and the results are inconsistent.[3,9,10] The first head-to-head real-world study compared the viral load dynamics of hospitalized COVID-19 patients with nirmatrelvir/ritonavir or azvudine at Beijing Youan Hospital, and the results showed that the patients who

received nirmatrelvir/ritonavir had a more rapid virus suppression and an earlier RT-PCR negative conversation during the initial phase of hospitalization than patients who received azvudine.[10] However, a retrospective study comparing clinical outcomes of two drugs found that azvudine was significantly associated with a lower risk of composite disease outcomes, especially in patients <65 years, with comorbidity, severe COVID-19 infection at admission, and receiving antibiotics.[9] The proportion of severe illness and death caused by COVID-19 among the elderly is the highest among all age groups, and elderly patients are commonly accompanied by multi-disease and multi-reuse drugs. The choice of drugs should be very cautious for super elderly patients with severe COVID-19 infection. In this study, we compared the antiviral effectiveness and short-term mortality among elderly patients with severe COVID-19 infection who received nirmatrelvir/ritonavir or azvudine to evaluate the clinical effectiveness of these two drugs in the elderly.

Methods

Study design and inclusion population

We conducted an observational study of elderly patients with severe COVID-19 infection who were admitted to the Second Medical Center of the People's Liberation Army General Hospital from December 2022 to January 2023 to compare the antiviral effectiveness and clinical outcomes of azvudine versus nirmatrelvir/ritonavir. We included elderly patients with COVID-19 infection who tested positive for RT-PCR at the Second Medical Center of the PLA General Hospital between December 2022 and January 2023. Inclusion criteria were as follows: (1) severe or critically COVID-19 patients; (2) aged ≥65 years. Patients with severe COVID-19 infection were defined as having any of the following: respiratory distress, RR ≥ 30 beats/min; oxygen saturation ≤93% at rest; Arterial partial oxygen pressure (PaO2)/oxygen absorption concentration (FiO2)≤300 mmHg; The clinical symptoms worsened progressively, and the lung imaging showed that the lesion progressed significantly >50% within 24–48 h. Critically, patients are defined as those with respiratory failure requiring mechanical ventilation or shock or other organ failure requiring intensive care. Exclusion criteria are as follows: (1) <65 years old; (2) patients with a mild or moderate COVID-19 infection; (3) patients with multiple organ failure or immunosuppressants. All eligible patients were divided into the non-antiviral group, azvudine group, and nirmatrelvir/ritonavir group according to the antiviral treatment they received.

Ethics

This study follows the STROBE Reporting Guidelines and has been approved by the PLA General Hospital Ethics Committee (S2022-797). The retrospective cohort study using anonymized data does not require patients' informed consent.

Baseline variable

The medical records of all enrolled patients were retrieved from the electronic medical record system of the PLA General Hospital, including age, sex, height, weight, and other demographic characteristics, date of onset of symptoms and hospitalization, prescription and drug allocation records, basic medical history and medications, concomitant therapy for this infection (such as corticosteroid therapy, immunoglobulin, antibiotics therapy etc.), clinical laboratory indicators at admission (C-reactive protein concentration (CRP), lymphocyte count, neutrophil count, platelet count, prothrombin time, D-dimer concentration, troponin, brain natriuretic peptide (BNP), etc.).

Follow-up and outcome

All elderly severe patients who received azvudine or nirmatrelvir/ritonavir during the observation period were defined as being exposed to antiviral treatments, allowing for combination therapy (such as antibiotics or corticosteroid therapy). The observation period is from the onset of symptoms to the date of registered death or the end of the observation period (March 30, 2023), whichever comes first.

The primary outcome of this study was composite outcomes of disease, including all-cause mortality, initiation of invasive mechanical ventilation, and transfer to the intensive care unit (ICU). The secondary outcome was defined as all-cause mortality. In addition, we documented emerging multisystem complications during hospitalization for COVID-19 infection, including myocardial injury/heart failure (HF), respiratory failure, and initiation of invasive mechanical ventilation. Confirming all complications relies on the results of imaging or laboratory tests recorded in the medical record system. Myocardial injury/HF is defined as new symptoms of HF and abnormal levels of BNP. The diagnosis of respiratory failure mainly depends on the arterial blood gas analysis results. Review the surgical records to determine whether invasive mechanical ventilation was initiated and record the date. In addition, the cycle threshold (Ct) value of SARS-CoV-2 RT-PCR was recorded for all patients during each follow-up period, and the detection limit of the Ct value was set at 40.

Statistical analysis

We used observational data to estimate the effectiveness of two antiviral drugs, azvudine and nirmatrelvir/ritonavir, in elderly severe patients with COVID-19. All patients who received antiviral drugs were divided into two groups by the type of antiviral drug received, which the doctor decided. Then we used propensity score models conditional on baseline covariates (age, sex,

history of disease, and clinical laboratory indicators at admission) with a caliper width of 0.02 to reduce the potential bias. We assess the characteristics of the baseline covariate by independent sample t-test for continuous variables and chi-square for classification variables both in the unmatched and propensity-score matched analytic cases. We also explored differences in the concomitant treatments received by the two groups throughout this infection. For continuous variables, the data is reported as mean ± standard deviation; for categorical variables, the data is reported as a percentage. A scatterplot of the Ct values of each group over time was plotted, and curve fitting was performed. All significance tests were double-tailed, with $p < 0.05$ considered statistically significant.

We defined March 30, 2023, as the end point of follow-up, and we compared the incidence of HF, respiratory failure, and other complications between the two groups using Poisson regression. In addition, we compare the survival curves using the Kaplan–Meier method and log-rank test. A Cox proportional risk model was constructed to analyze the relationship between antiviral interventions and outcomes. A sequential model was established. Model 1 is the unadjusted model. Model 2 was adjusted for age, sex, history of hypertension, dyslipidemia, chronic lung disease, heart disease, diabetes, stroke, malignancy, and the duration between the onset of symptoms and hospitalization. Due to the comparison of multiple outcomes, Bonferroni's correction for multiple comparisons was applied to avoid an increased probability of type 1 error. A two-sided p-value of 0.025 (0.05/2) was taken to indicate statistical significance. Finally, we estimated the statistical power analysis of our ability to detect a difference in clinical outcomes between patients who are receiving azvudine or nirmatrelvir/ritonavir; we determined that we had 80% power to detect a 24% difference in clinical outcomes.

To explore the efficacy of antiviral drugs more directly, we compared we compared the Ct value curve and clinical outcomes of all enrolled patients, including the no antiviral group, azvudine recipients and nirmatrelvir/ritonavir recipients. Given that most patients with severe infection who did not receive antiviral therapy had contraindications, we did not match this group. All statistical analyses were performed using SPSS 27 and R software (version 4.1.2).

Role of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From December 2022 to January 2023, 364 patients with SARS-CoV-2 infection were admitted to the Second Medical Center of the PLA General Hospital, of whom 12 patients were under 65 years old at the time of diagnosis, 93 patients with a mild condition, 10 patients received three antiviral drugs including azvudine, nirmatrelvir/ritonavir, and molnupiravir in a different order. After excluding all the above cases, a total of 249 elderly patients with severe COVID-19 infection who were over 65 years old with complete clinical data and medication information were included in the study, including 128 azvudine recipients, 66 nirmatrelvir/ritonavir recipients and 55 patients not received antiviral treatments (Fig. 1). The mean age of all included patients was 91.41 (7.57) years old, and the highest age was 108 years old (Supplementary Fig. S1). Treatment groups and baseline information for all patients are presented in Supplementary Table S1.

We performed a propensity-score-match of two groups of patients receiving azvudine or nirmatrelvir/ritonavir. After matching propensity scores, 116 patients were included in the final analysis. We compared age, sex, laboratory indicators such as neutrophils, lymphocytes, CRP, fasting blood glucose, creatinine, prothrombin time and D-dimer levels at admission, and medical history in two groups (Table 1). Before matching, there were no significant differences in all indicators between the two groups, but after matching, the age of nirmatrelvir/ritonavir recipients was significantly higher than that of azvudine recipients (90.48 (9.04) vs 86.98 (8.77), $p = 0.036$). In addition, it is worth noting that patients in the azvudine group had a significantly longer interval from onset of symptoms to hospitalization than those in the nirmatrelvir/ritonavir group both before and after matching. We also analyzed the concomitant treatments of the two groups during this infection, and the result showed that there were no significant differences between the azvudine and nirmatrelvir/ritonavir groups in the proportion of need for corticosteroid therapy, immunoglobulin, antibiotic use, and combination. However, the duration of corticosteroid use was higher in the nirmatrelvir/ritonavir group than in the azvudine group (8.03 (8.07) vs 12.28 (12.67), $p = 0.034$), and the results were consistent in before and after matching (Table 1). The trend of the Ct value curve of all groups increased slowly; the rate of viral decline in the early stages of the nirmatrelvir/ritonavir group was better than that of the azvudine group, and the rate was the lowest in the non-antiviral group. However, none of the three trends were significant (Fig. 2).

At the end of the follow-up, 77 patients died in all three groups and 27 patients died in two antiviral drug groups after propensity score matching during a mean follow-up period of 83.91 days. We calculated the crude incidence rate of complications and received invasive mechanical ventilation during this hospitalization and compared the incidence rate ratio for the complication variables between the two groups using Poisson regression with the adjustment for the differing lengths

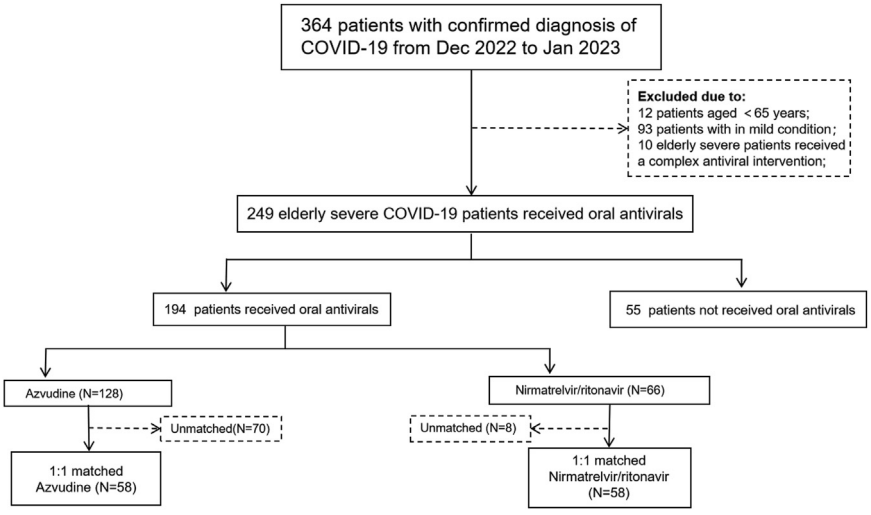

Fig. 1: Study profile.

of follow-up for each patient (Table 2). The results showed that the invasive mechanical ventilation rate of nirmatrelvir/ritonavir was 1.20 times higher than that of azvudine.

Kaplan–Meier method and log-rank test were used to compare the outcome events of different antiviral intervention groups. The risk of the composite outcome was significantly lower with azvudine than with

Baseline variable	Before matching			After 1:1 propensity score matching		
	Azvudine	Nirmatrelvir/ritonavir	p-value	Azvudine	Nirmatrelvir/ritonavir	p-value
N	128	66		58	58	
Age	91.29 ± 7.57	90.73 ± 8.74	0.643	86.98 ± 8.77	90.48 ± 9.04	0.036
Sex (male)	121 (94.5%)	62 (93.9%)	0.866	53 (91.4%)	54 (93.1%)	0.729
Laboratory abnormalities						
Neutrophil	0.74 ± 0.13	0.71 ± 0.13	0.180	0.69 ± 0.14	0.72 ± 0.12	0.145
Leukomonocyte	0.17 ± 0.11	0.18 ± 0.11	0.715	0.21 ± 0.11	0.18 ± 0.11	0.137
C-reactive protein, median (IQR)	4.51 (1.25–6.56)	3.44 (1.40–6.60)	0.542	2.53 (0.66–5.89)	3.60 (1.59–7.18)	0.480
Fasting blood-glucose	8.02 ± 3.52	8.29 ± 4.68	0.646	7.79 ± 3.77	8.21 ± 4.62	0.592
Creatinine, median (IQR)	84.00 (67.40–120.23)	91.50 (74.50–123.53)	0.220	82.95 (63.75–110.95)	93.50 (75.25–123.53)	0.587
Prothrombin time	16.40 ± 1.45	16.45 ± 2.33	0.870	16.64 ± 1.68	16.41 ± 2.44	0.560
D-dimer, median (IQR)	1.48 (0.96–2.81)	1.47 (0.82–2.81)	0.484	1.37 (0.87–2.81)	1.54 (0.83–2.81)	0.887
Duration between onset of symptoms and hospitalization	3.02 ± 3.99	1.08 ± 2.62	<0.001	3.30 ± 4.42	1.09 ± 2.66	0.001
Comorbidity						
Hypertension	103 (80.5%)	52 (78.8%)	0.782	39 (67.2%)	48 (82.8%)	0.054
Respiratory	53 (41.4%)	28 (42.4%)	0.892	20 (34.5%)	24 (41.4%)	0.444
Cardiovascular diseases	95 (74.2%)	55 (83.3%)	0.151	39 (67.2%)	48 (82.8%)	0.054
Diabetes mellitus	49 (38.3%)	34 (51.5%)	0.078	24 (41.4%)	27 (46.6%)	0.575
Cerebrovascular diseases	60 (46.9%)	31 (47.0%)	0.990	19 (32.8%)	27 (46.6%)	0.129
Medication use						
Need for corticosteroid therapy	91 (71.1%)	54 (81.8%)	0.103	37 (63.8%)	46 (79.3%)	0.064
Duration of corticosteroid therapy	8.46 ± 7.68	11.98 ± 12.03	0.014	8.03 ± 8.07	12.28 ± 12.67	0.034
Need for immunoglobulin	70 (54.7%)	36 (54.5%)	0.985	28 (48.3%)	29 (50.0%)	0.853
Duration of immunoglobulin	4.34 ± 5.67	5.02 ± 6.34	0.449	3.83 ± 5.06	4.52 ± 6.32	0.518
Need for antibiotics	125 (97.7%)	65 (98.5%)	0.700	55 (94.8%)	57 (98.3%)	0.309
Need for a combination of antibiotics	88 (68.8%)	49 (74.2%)	0.426	34 (58.6%)	41 (70.7%)	0.174

IQR: inter-quartile range.

Table 1: **Baseline characteristics of elderly patients with COVID-19 receiving either azvudine or nirmatrelvir/ritonavir.**

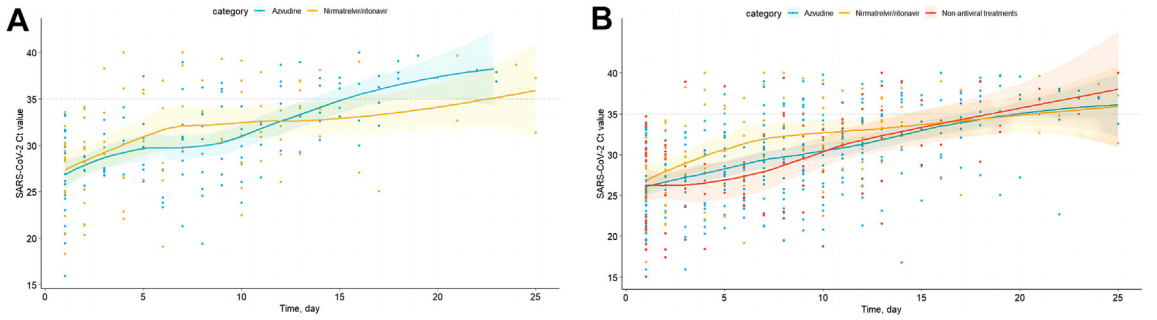

Fig. 2: Scatter plot of serial cycle threshold (Ct) values of elderly patients with COVID-19. Blue circles indicate patients received azvudine. Yellow circles indicate patients received nirmatrelvir/ritonavir. Red circles indicate patients who did not receive antiviral therapy. The full thick curves represent the fitting curve for each group. The shaded areas indicate 95% credible intervals of the associated curve and their bounds. (A) Patients receiving azvudine, nirmatrelvir/ritonavir after propensity-score-matching (B) patients receiving azvudine, nirmatrelvir/ritonavir or non-antiviral treatments.

nirmatrelvir/ritonavir, even if Bonferroni's correction for multiple comparisons was applied (log-rank p = 0.020) (Fig. 3A), but the risk of all-cause mortality did not differ significantly between the two groups (Fig. 3B). In Cox proportional regression analysis, the risk ratio was still statistically significant after adjusting for some single confounders (Supplementary Table S2), but the multi-adjusted Cox proportional hazard model showed that there is no significant correlation between antiviral interventions and the composite outcomes or all-cause mortality (Table 3). The composite outcomes of patients in the azvudine group were consistent with hazard ratios ranging from 0.805 (lower risk of outcomes) to 3.488 (higher risk of outcomes), and the all-cause mortality of patients in azvudine group was consistent with hazard ratios ranging from 0.546 (lower risk of death) to 3.051 (higher risk of death). In addition, we included patients who did not receive any antiviral to explore the clinical benefit of antiviral drugs, and the Kaplan–Meier survival analysis suggested that neither nirmatrelvir/ritonavir nor azvudine demonstrated a survival benefit. We also did a Cox analysis of the outcomes of the three groups of patients, and the results showed that the risk of death was 0.730 (0.423–1.262) in the azvudine group 0.802 (0.435–1.480) and in the nirmatrelvir/ritonavir group compared with the non-antiviral group.

In subgroup analysis, participants were grouped by age (90 years old as category boundary), cerebrovascular diseases, or diabetes and categorized by antiviral drugs. Fig. 4 shows the results of a multivariate Cox regression analysis of the association between composite outcomes, all-cause death, and antiviral drugs in all hierarchical groups. After controlling all potential covariates, there was no significant correlation between different antiviral interventions and outcomes in all subgroups except the cerebrovascular disease subgroup. Nirmatrelvir/ritonavir treatment was significantly associated with a higher risk of composite outcomes in patients with a history of cerebrovascular disease (HR:4.430, 95%CI:1.332–14.726), but this may merely be a false positive result from multiple comparisons.

Discussion

Due to the change in epidemic prevention policy, large-scale COVID-19 infections occurred intermittently in China. In the first infection wave in December 2022, azvudine and nirmatrelvir/ritonavir were the priority antiviral drugs recommended by the People's Republic of China's National Health Commission published the Scheme for Diagnosis and Treatment of SARS-CoV-2 (The 10th Trial Edition). Several studies have verified the effectiveness of azvudine and nirmatrelvir/ritonavir

Variable	Azvudine (N = 58)			Nirmatrelvir/ritonavir (N = 58)		
	n (%)	Rate per 100 person-days	IRR (95% CI)	n (%)	Rate per 100 person-days	IRR (95% CI)
Myocardial injury/heart failure	25 (43.1%)	0.74	Reference	29 (50.0%)	0.96	1.329 (0.779–2.285)
Respiratory failure	18 (31.0%)	0.45	Reference	25 (43.1%)	0.70	1.578 (0.863–2.935)
Invasive mechanical ventilation	10 (17.2%)	0.21	Reference	18 (31.0%)	0.46	2.197 (1.034–4.948)

IRR: incidence rate ratio; 95% CI: 95% confidence interval.

Table 2: **Poisson regression analysis complications occurred between elderly severe patients receiving either azvudine or nirmatrelvir/ritonavir.**

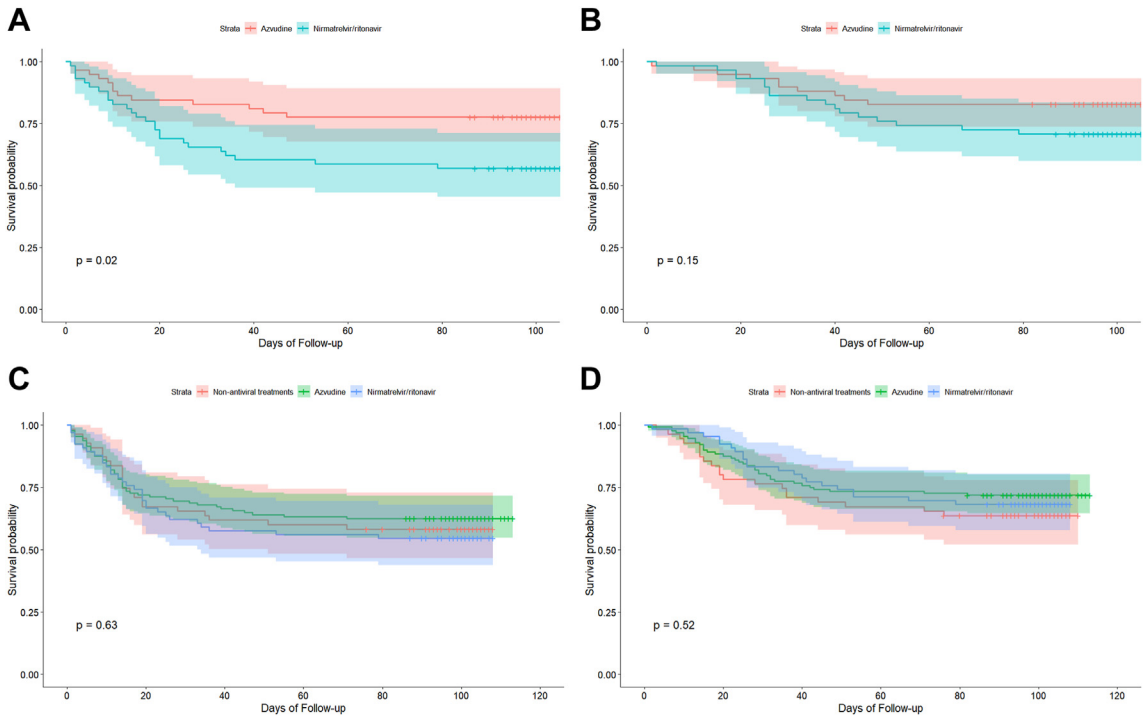

Fig. 3: Kaplan–Meier time-to-event curves of elderly patients with COVID-19. (A) Composite outcomes of patients receiving azvudine, nirmatrelvir/ritonavir after propensity-score-matching. (B) All-cause death of patients receiving azvudine, nirmatrelvir/ritonavir. (C) Composite outcomes of patients receiving azvudine, nirmatrelvir/ritonavir or non-antiviral treatments. (D) All-cause death of patients who receive azvudine, nirmatrelvir/ritonavir or non-antiviral treatments. $p < 0.025$ was considered statistically significant after Bonferroni's correction.

Groups	N	Event N (%)	Model 1	Model 2
			Crude HR (95% CI)	Adjusted HR (95% CI)
Two antiviral drug groups after propensity-score-match				
Composite outcome				
Azvudine	58	13 (22.41%)	Reference	Reference
Nirmatrelvir/ritonavir	58	25 (43.10%)	2.165 (1.107–4.235)[a]	1.676 (0.805–3.488)
All-cause death				
Azvudine	58	10 (17.2%)	Reference	Reference
Nirmatrelvir/ritonavir	58	17 (29.3%)	1.769 (0.810–3.864)	1.291 (0.546–3.051)
All three groups				
Composite outcome				
Non-antiviral treatments	55	23 (41.8%)	Reference	Reference
Azvudine	128	48 (37.5%)	0.896 (0.545–1.472)	0.970 (0.585–1.608)
Nirmatrelvir/ritonavir	66	30 (45.5%)	1.118 (0.649–1.924)	1.222 (0.698–2.139)
All-cause death				
Non-antiviral treatments	55	20 (36.4%)	Reference	Reference
Azvudine	128	36 (28.1%)	0.730 (0.423–1.262)	0.799 (0.457–1.395)
Nirmatrelvir/ritonavir	66	21 (31.8%)	0.802 (0.435–1.480)	0.868 (0.463–1.630)

Model 1: Crude model. Model 2: Adjusted for age, sex, history of hypertension, dyslipidemia, chronic lung disease, heart disease, diabetes, cerebrovascular diseases and malignancy and duration between onset of symptoms and hospitalization. HR: Hazard Ratio; 95% CI: 95% confidence interval. [a]Statistical significance after Bonferroni's correction.

Table 3: **Cox proportional hazards regression analysis of different antiviral treatment and clinical outcomes.**

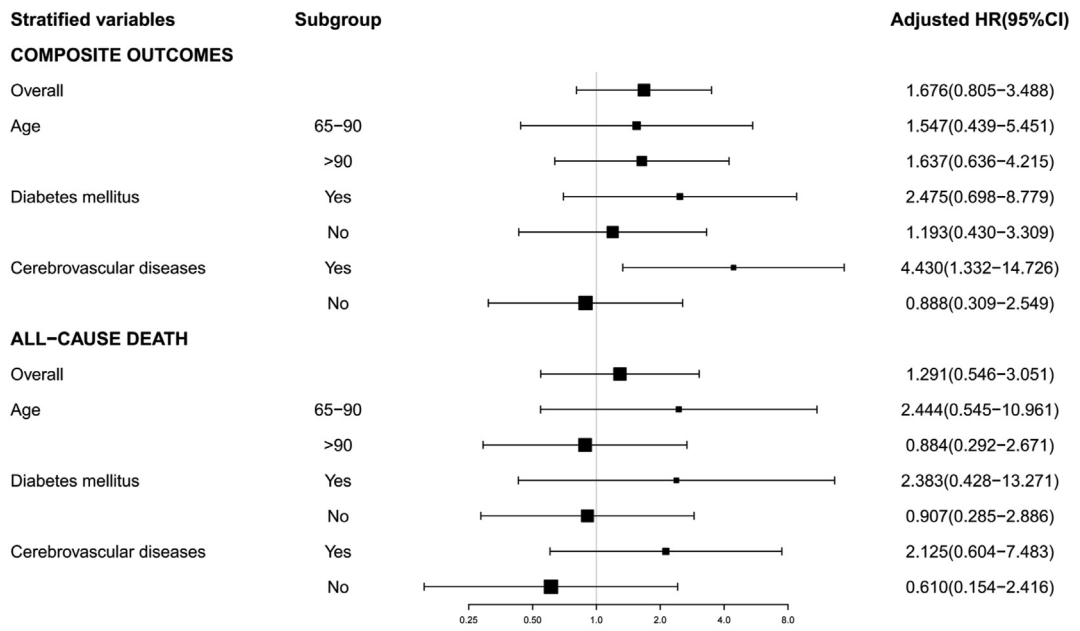

Fig. 4: Subgroup analyses for the association between composite outcomes, all-cause death and different antiviral treatments in the 58 propensity-score-matched pairs. Abbreviation: HR: Hazard Ratio; 95% CI: 95% confidence interval.

in adult COVID-19 patients.[4,8,11] The efficacy of nirmatrelvir/ritonavir in the elderly population is still controversial. The well-known EPIC-HR trial evaluated the safety and effectiveness of nirmatrelvir/ritonavir in non-hospitalized adults with mild-to-moderate COVID-19, and this conclusion is robust in the stratified analysis of different age groups with 65 years old as the cutoff.[7] Studies have reported that nirmatrelvir/ritonavir recipients do not show significant clinical benefits compared with controls in people under 65 years old.[12,13] Another study in the United States reached the clinical outcome of veterans over 65 years old with mild to moderate SARS-CoV-2 infection who received and did not receive nirmatrelvir/ritonavir treatment. The result showed that nirmatrelvir/ritonavir intervention was associated with a lower 30-day hospitalization or mortality,[14] suggesting that elderly patients with nirmatrelvir/ritonavir intervention had more excellent clinical benefits than young people. A simulation study of the actual effectiveness of nirmatrelvir/ritonavir in COVID-19 hospitalized patients during the Omicron outbreak found no significant interaction between age and nirmatrelvir/ritonavir treatment.[15] The effectiveness of azvudine also has been demonstrated in real-world studies.[3,8] The result of a single-center, retrospective cohort study showed that azvudine was associated with a significantly reduced risk of composite progressive outcomes, especially in males and severe patients with COVID-19.[8] A meta-analysis of five randomised controlled trials found that azvudine can hasten the clinical symptoms of patients with COVID-19 and RT-PCR negative without the burden of side effects.[5]

Previous studies have confirmed the benefits of azvudine and nirmatrelvir/ritonavir for hospitalization or death, taking into account the ages,[16–18] but the results of the comparative analysis of the two drugs are not complete. Meanwhile, elderly patients are commonly accompanied by multi-disease and multi-reuse drugs.[19] The elderly need to choose antiviral drugs more carefully due to the limitations of complications and drug interaction. There is an urgent need to explore the applicability of the previous findings in elderly severe patients to assist in clinical decision-making. In this retrospective cohort study, we found that there was no statistical difference in antiviral effectiveness and clinical outcomes between patients treated with nirmatrelvir/ritonavir or azvudine in elderly patients with severe COVID-19 infection, although patients who received nirmatrelvir/ritonavir may be older, have longer interval from the onset of symptoms to hospitalization and seemly more severe pulmonary involvement compared with patients who received azvudine because of their prolonged duration and elevated rate of receiving corticosteroid therapy.

The results showed a potential inferior antiviral effectiveness of azvudine, which several studies have demonstrated.[10,20] Gao et al. found that patients receiving nirmatrelvir/ritonavir showed faster viral inhibition and earlier RT-PCR-negative conversion at the initial hospitalization stage than patients who received azvudine.[10] Another study from Tibet also found that nirmatrelvir/ritonavir could suppress the virus more rapidly for patients with mild COVID-19.[20] Pathologically, patients with high viral load are prone to severe

diseases, and early inhibition of viral replication would significantly improve the prognosis of patients,[21,22] but our research shows the opposite trend. Cox analysis showed a trend of increased risk of clinical outcomes in nirmatrelvir/ritonavir recipients, although there was no statistical significance.

We speculate there may be many reasons for the early favorable antiviral trend and the seemingly poor survival outcome of nirmatrelvir/ritonavir. One possible reason is the difference in the indications and usage of the two drugs. The People's Republic of China's National Health Commission published the Scheme for Diagnosis and Treatment of SARS-CoV-2 (The 10th Trial Edition), which approved the use of nirmatrelvir/ritonavir authorization for the treatment of high-risk patients with mild to moderate COVID-19 for five days. Azvudine is recommended for treating adult patients with moderate COVID-19 infection for 14 days. Super-elderly people with an average age of 91.41 included in this study have weak anti-viral abilities, and almost all suffer from more than two chronic diseases. Virus infection may cause an acute state of their primary chronic diseases, resulting in prolonged illness. Therefore, we tried to speculate that early use of nirmatrelvir/ritonavir may inhibit early replication of the virus in cells, but a longer course of antiviral therapy with azvudine may lead to better clinical outcomes in super-elderly patients with COVID-19 infection. Secondly, the severe/critical infection status of the patients included in this study may also have contributed to this result. Cao et al. reported an analysis of combined treatment in 1082 severely and critically ill patients with COVID-19. The results showed that azvudine and nirmatrelvir/ritonavir significantly reduced 60-day mortality compared with the control group, with a probability of improving 2-month survival of 99.8% and 91.9%, respectively. Nirmatrelvir/ritonavir seems to have a lower probability of improving 2-month survival.[23] Another open-label, multicenter, randomized controlled trial indicated that nirmatrelvir/ritonavir showed no significant reduction in the risk of all-cause mortality on day 28 and the duration of SARS-CoV-2 RNA clearance in which hospitalized adult patients with severe comorbidities.[24] Therefore, patients' critical status may also be responsible for the early favorable antiviral trend and seemingly poor survival outcome of nirmatrelvir/ritonavir in this study. Finally, the cause of selection bias cannot be ruled out because patients with more severe clinical presentations may have been preferentially selected by clinicians to receive nirmatrelvir/ritonavir. In that case, patients who received nirmatrelvir/ritonavir would be expected to have worse outcomes, which could obscure a potential therapeutic benefit of nirmatrelvir/ritonavir. The two groups matched well on most clinical factors, but patients who received nirmatrelvir/ritonavir may be older, have longer intervals from the onset of symptoms to hospitalization and prolonged duration and elevated rate of receiving corticosteroid therapy compared with patients who received azvudine.

This is a potential bias that can't be controlled in real-world studies, and we try to prevent or mitigate this bias by propensity-score-matching, but we can't eliminate it. It is worth noting that neither nirmatrelvir/ritonavir nor azvudine demonstrated a survival benefit compared to patients who did not receive any antivirals. This lack of clinical benefit might be attributed to potential bias.

To the best of our knowledge, this is the first study to evaluate the clinical effectiveness of azvudine and nirmatrelvir/ritonavir in such elderly patients with severe COVID-19 by real-world clinical evidence. We hope our findings can provide a reference for the selection and prioritisation of antiviral drugs in extremely elderly patients with severe COVID-19 infection. Our study also has some limitations. The first and most important of which is non-randomised treatment selection arising from the retrospective design of the study. Although our data are collected continuously, and some potential confounding factors are corrected, we cannot completely avoid the selection bias that may exist in the retrospective study. In addition, the sex ratio in this study is uneven; only a small number of women (6%) was included due to the medical institutions. Second, this study only included super-elderly patients with severe COVID-19. Third, we did not get the relevant data on vaccination. Finally, we only had a median short-term follow-up of about three months and did not evaluate the long-term efficacy of the two drugs.

In this retrospective study, primarily involving critically ill elderly patients, azvudine showed a similar antiviral effectiveness and survival outcomes with nirmatrelvir/ritonavir. When compared to patients who did not receive any antivirals, neither nirmatrelvir/ritonavir nor azvudine demonstrated a survival benefit. This lack of clinical benefit might be attributed to potential bias. This single-institution study may not be adequately powered to detect the effect of different antiviral drug, thus inferences must be drawn from the study findings with considerable caution.

Contributors

SW, JS, and XZ proposed the idea and drafted the manuscript. ML, BQ, SW and TZ completed the quality control of clinical data. ML and NZ contributed to data analysis. WZ, CM, DX, YB, GQ, LL, HS, BZ, KL, BY, SL, FW, JM, LZ, YW, LA, WL, QC, RZ, XY, YY, QA, QM, SY, HH, PS, LG, WL, LX, LL, and KW collected clinical data. QZ, QS, ZZ, and XF conducted project integration. YH, TL and PZ contributed to the conception of the study and helped perform the revision with constructive discussions. All authors read and approved the final version of the manuscript. All authors verified the underlying data of this study, had full access to all the data in the study and accepted responsibility for the decision to submit for publication.

Data sharing statement

All data could be requested from the corresponding author. Qualified researchers should submit a proposal to the corresponding author outlining the reasons for requiring the data. The use of data must also comply with the requirements of our institutes. A signed data access

agreement with the sponsor is required before accessing shared data. Patient-level data will not be made available.

Declaration of interests

All the authors declared no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102468.

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