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ORIGINAL RESEARCH

Is Azvudine Comparable to Nirmatrelvir-Ritonavir in Real-World Efficacy and Safety for Hospitalized Patients with COVID-19? A Retrospective Cohort Study

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ABSTRACT

Introduction: Azvudine and nirmatrelvir-ritonavir are more extensively used to treat COVID-19 in China due to their earlier approval by the National Medical Products Administration. However, there has been a scarcity of research directly comparing the clinical outcomes between azvudine and nirmatrelvir-ritonavir till now. We aimed to make a head-to-head comparison of the efficacy and safety of azvudine or nirmatrelvir-ritonavir in hospitalized patients with COVID-19 in China.

Methods: This retrospective cohort study was conducted using data collected from Tongde Hospital of Zhejiang Province between Decem-

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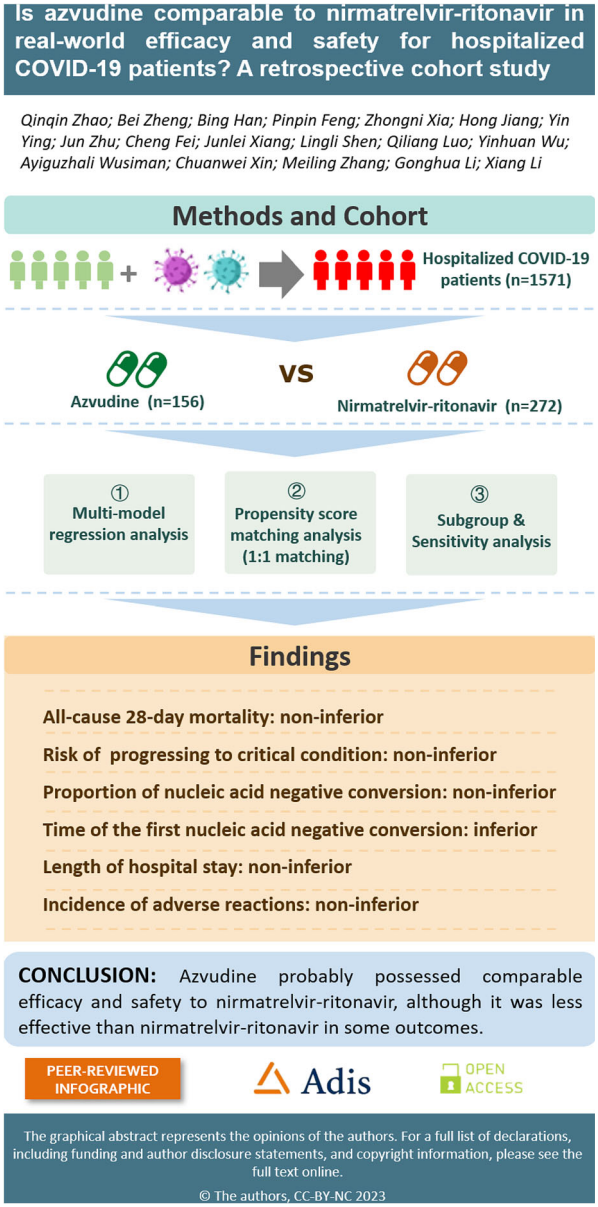
ber 2022 and January 2023. All-cause mortality, risk of progressing to a critical condition, proportion with nucleic-acid negative conversion (P_{NANC}), time to first nucleic-acid negative conversion (T_{FNANC}), length of hospital stay and incidence of adverse events were systematically assessed as outcomes. Multi-model regression analysis, propensity-score-matching analysis, subgroup analysis and several sensitivity analyses were applied to compare these outcomes.

Results: This study included a total of 1571 hospitalized patients with COVID-19, among whom 272 received nirmatrelvir-ritonavir and 156 received azvudine. We found no significant differences in all-cause mortality (HR 1.41; 95% CI 0.56–3.56; $P = 0.471$), risk of progressing to critical COVID-19 (HR 1.67; 95% CI 0.78–3.60; $P = 0.189$), P_{NANC} (HR 0.87; 95% CI 0.69–1.09; $P = 0.220$), length of stay (β − 0.82; 95% CI − 2.78 to 1.15; $P = 0.414$) and adverse event rate (3.21% vs. 4.41%, $P = 0.538$) between the two groups, although azvudine was slightly less effective than nirmatrelvir-ritonavir. Meanwhile, the azvudine group exhibited a significantly longer T_{FNANC} (β 2.53; 95% CI 0.76–4.29; $P = 0.005$) than the nirmatrelvir-ritonavir group. Results were similar for propensity-score matching and multiple sensitivity analyses.

Conclusion: Azvudine probably possessed comparable efficacy and safety to nirmatrelvir-ritonavir, although it was less effective than nirmatrelvir-ritonavir for some outcomes.

Graphical Abstract:



Keywords: COVID-19; Azvudine; Nirmatrelvir-ritonavir; Real-world; Clinical outcome

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Key Summary Points

Why carry out this study?

Chinese guidelines prioritize the use of azvudine and nirmatrelvir-ritonavir in patients with COVID-19.

There has been a scarcity of research directly comparing clinical outcomes between azvudine and nirmatrelvir-ritonavir till now.

Is azvudine comparable to nirmatrelvir-ritonavir in real-world efficacy and safety for hospitalized patients with COVID-19?

What was learned from the study?

Azvudine is potentially non-inferior to nirmatrelvir-ritonavir in the outcomes of 28-day mortality, risk of progression to a critical condition, P_{NANC}, length of hospital stay, and incidence of adverse reactions.

Azvudine had a longer nucleic-acid negative conversion time vs. nirmatrelvir-ritonavir.

The study supports the routine use of azvudine in hospitalized patients with COVID-19.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.23608389.

INTRODUCTION

Public health and economic systems are facing a tremendous burden globally, which can be attributed to the ongoing COVID-19 pandemic [1]. At the end of 2022, China had just suffered an intense wave of COVID-19 caused by the current dominant strain, Omicron, which showed high transmissibility and immunologic escape [2, 3]. Early initiation of antivirals brought the pandemic under control by reducing the risks of mortality and disease progression. Although numerous drugs have been developed, there are still very few approved antivirals available for COVID-19 [4]. Unlike in other countries, azvudine and nirmatrelvir-ritonavir were more extensively used during the winter 2022 epidemic in China due to their earlier approval by the National Medical Products Administration (NMPA) than other antivirals [5, 6].

Nirmatrelvir-ritonavir has been authorized for emergency use by many countries [7]. In China, it had been granted conditional approval for the treatment of non-hospitalized patients with COVID-19 with mild to moderate symptoms since February 2022 [5]. According to the EPIC-HR trial, nirmatrelvir-ritonavir reduced hospitalization and mortality rates by approximately 88% when initiated within 5 days of symptom onset compared to placebo [8]. Besides, its efficacy and safety have been extensively researched in other real-world studies, including comparisons with control groups [9–11] or other antivirals [12–16]. However, several concerns remain regarding the use of nirmatrelvir-ritonavir, including multiple drug–drug interactions [17] and a rebound of COVID-19 after antiviral treatment cessation [18].

Azvudine, another promising antiviral against COVID-19, was previously approved as an anti-HIV drug [19]. It was granted conditional authorization by the NMPA to treat COVID-19 in China on July 25, 2022 [6]. Unfortunately, limited published information is available regarding the use of azvudine in clinical practice. In a preliminary randomized controlled trial (n = 20), azvudine showed a shorter time to first nucleic-acid negative conversion (T_{FNANC}) vs. placebo [20]. Further phase 3 multicenter randomized placebo-controlled studies demonstrated that patients with COVID-19 who received azvudine had a lower viral load, a shorter time to symptom improvement, and a

lower risk of progression or death vs. control [21, 22]. Although there are some acceptable efficacy and safety profiles of azvudine for treating COVID-19, evidence investigating its real-world outcomes is scarce. Only three real-world reports that compare azvudine with placebo have been published [23] or posted on the MedRxiv website for public comment [24, 25].

To date, there have been limited comparative studies between azvudine and nirmatrelvir-ritonavir, except for two studies that focused on viral load dynamics or other clinical efficacy outcomes [26, 27]. Therefore, a comparison of azvudine and nirmatrelvir-ritonavir is urgently needed. In this retrospective cohort study, we aimed to make a systematic head-to-head comparison of the efficacy and safety of azvudine and nirmatrelvir-ritonavir in hospitalized adult patients with COVID-19 in China. We hypothesized that azvudine is comparable to nirmatrelvir-ritonavir in real-world efficacy and safety for hospitalized patients with COVID-19.

METHODS

Study Design and Participants

We conducted a retrospective cohort study of hospitalized patients with COVID-19 in Tongde Hospital of Zhejiang Province who were prescribed azvudine or nirmatrelvir-ritonavir between December 20, 2022 and January 31, 2023. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tongde Hospital in Zhejiang Province (acceptance number: 2023-015(K)). Informed consent was exempted due to its retrospective nature. This research adheres to the STROBE reporting guidance. We obtained most of the data from the electronic medical record system, while some missing data were obtained through telephone follow-ups. Patients were admitted to the hospital with a COVID-19 diagnosis based on positive SARS-CoV-2 nucleic acid testing by RT-PCR and a minimum follow-up period of 28 days. Patients were considered to qualify for inclusion if they had taken nirmatrelvir-ritonavir or azvudine within 5 days of their COVID-19 diagnosis and they exhibited mild-to-moderate or severe symptoms that may benefit from antiviral therapy. The index date was defined as the diagnosis date (day 0). We excluded patients who had not received nirmatrelvir-ritonavir or azvudine within 5 days of diagnosis establishment; those under the age of 18; those who have previously taken other antivirals; and individuals with drug contraindications for nirmatrelvir-ritonavir or azvudine, such as severe renal impairment (CrCl < 30 mL/min), severe liver disorder, or those taking concurrent interacting drugs which are contraindicated.

Procedures

The decision to initiate antiviral treatment was ultimately made by patients and clinicians based on clinical features and guidelines. Nirmatrelvir-ritonavir was administered orally as 300 mg nirmatrelvir plus 100 mg ritonavir (twice daily) for 5 days, while azvudine was dosed as 5 mg once daily for 7 or more days (not exceeding 14 days), with both doses adjusted according to renal function if necessary. Other treatments, such as prone ventilation, glucocorticoid therapy, nutrition support, and anticoagulant therapy, were also available. Demographic and clinical data were gathered prior to the prescription of antivirals, including age, sex, body mass index (BMI), COVID-19 severity level, medical history (diabetes, cardiovascular disease, chronic lung disease, tumor and immunosuppression), and smoking and drinking habits, as well as laboratory results such as lymphocyte count (LTM), D-dimers, and C-reactive protein (CRP) levels. These variables were considered covariates for analysis. Follow-up assessments were conducted for a maximum of 28 days to document and assess the clinical efficacy and adverse effects of the medications, apart from the T_{FNANC} and length of hospital stay outcomes, which necessitated additional follow-up beyond 28 days for certain patients. Patients were monitored from the index date until the occurrence of the outcome event, loss to follow-up, or the end of the observation period (February 28, 2023), whichever came first.

Variable Definitions

We established the severity of COVID-19 disease in accordance with the Chinese diagnosis and treatment protocol for COVID-19 infection (version 10) [28] (Supplementary Table S1). The definition of cardiovascular disease encompassed congestive heart failure, atherosclerotic heart disease, cerebrovascular disease, hypertension, or other cardiac conditions. Chronic lung disease was defined as chronic obstructive pulmonary disease, asthma, chronic bronchitis, or any structural lung diseases apart from bronchogenic carcinoma. A history of tumor and immunosuppression was defined as the presence of solid or hematologic malignancy, ongoing immunosuppressive treatment, HIV infection, previous solid organ transplant, or other related conditions. Smoking or drinking status was categorized into two groups: current and never/former smokers or drinkers. The proportion of nucleic-acid negative conversion (P_{NANC}) was defined as the ratio of those who tested negative to all patients in each group at a specific point during follow-up.

Outcomes

The primary outcome was all-cause 28-day mortality. The secondary outcomes were the risk of progression to a critical condition within 28 days. Other secondary outcomes included 28-day P_{NANC}, T_{FNANC}, length of hospital stay, and any adverse reactions associated with nirmatrelvir-ritonavir or azvudine. During the clinical study, all outcome events were meticulously documented and recorded.

Statistical Analysis

Continuous variables were presented as means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on the data distribution. Categorical variables were described using numerical values and their corresponding frequencies. Baseline characteristics were compared and summarized using Student's *t*-test, the Mann–Whitney *U* test, χ^2 tests, or Fisher's exact test, as appropriate. The assumption of missing at random was made, and multiple imputations were employed to account for missing data on BMI, LTM, D-dimer and CRP. We applied the R package "MICE" to execute this approach, resulting in a total of five imputed datasets.

Hazard ratios (HRs) with 95% CIs for some outcomes (all-cause mortality, risk of progression to a critical condition, and P_{NANC}) were estimated using time-dependent Cox regression models, with primary analyses employing a log-rank test along with Kaplan–Meier survival function estimates. For continuous outcomes (T_{FNANC} and length of hospital stay), we used linear regression models presented as β coefficients and their corresponding 95% CIs. For the T_{FNANC} outcome, patients who died or were lost before achieving negative results were excluded from analysis, and patients who passed away during hospitalization were excluded from the analysis of length of hospital stay. The variables included in the regression models were those that showed a significant relationship in univariate analysis ($p < 0.1$) or were deemed important based on existing literature and clinical judgment. Finally, three regression models were estimated: model 1, which was adjusted for age, sex, BMI, and severity of COVID-19; model 2, which was additionally adjusted for diabetes, cardiovascular disease, chronic lung disease, tumor and immunosuppression; and model 3, which was further adjusted for LTM, D-dimer and CRP in addition to the variables in model 2.

We conducted a secondary analysis utilizing propensity-score matching (PSM) to generate comparable cohorts for outcome analysis. Patients were matched in a 1:1 ratio using a logistic model and nearest-neighbor matching method with a caliper value of 0.1. The following covariates were selected to construct the propensity score: age, sex, BMI, COVID-19 severity, smoking and drinking status, diabetes mellitus, cardiovascular disease, chronic lung disease, tumor and immunosuppression history, LTM level, D-dimer concentration and CRP level. The PSM analysis was performed using the "MatchIt" package in R software.

We performed subgroup analyses based on the following characteristics when interactions

were detected: age (above and below 65 years), sex, BMI (above and below 24), COVID-19 severity, smoking status, alcohol consumption, diabetes, cardiovascular disease, chronic lung disease, and tumor and immunosuppression history.

Sensitivity analyses were carried out initially by constructing multilevel regression models and subsequently by replicating all analyses using the complete dataset without employing multiple imputations. A two-tailed *P* value of less than 0.05 indicated statistical significance. Statistical analyses were done using R4.2.1.

RESULTS

Overall, 1571 patients with confirmed COVID-19 were admitted to our hospital, among whom we identified 495 patients who received nirmatrelvir-ritonavir or azvudine. Of these participants, we excluded 25 individuals who initiated antiviral treatment beyond 5 days after symptom onset, 15 with outcomes of death or critical illness occurring less than 3 days after therapy initiation, 5 participants who had previously taken antivirals before the study, 2 with drug contraindications, 7 with severe renal diseases, 2 with severe liver diseases, and 11 individuals who were lost to follow-up. Finally, a total of 428 participants were included in the final analysis, comprising 272 nirmatrelvir-ritonavir recipients and 156 azvudine recipients (Fig. 1).

As shown in Table 1, the majority of the baseline characteristics were well balanced between the two groups prior to matching. The mean age of the participants was 77.31

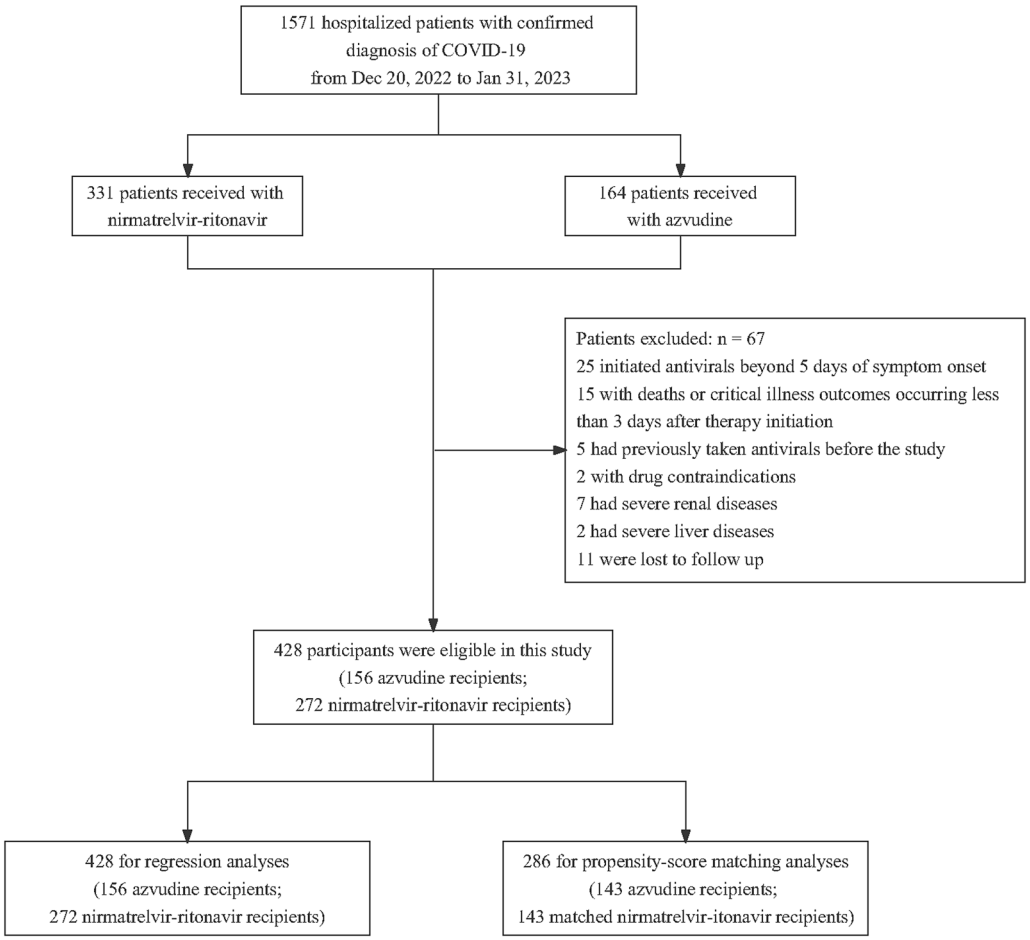


Fig. 1 Study participant flowchart

Table 1 Baseline characteristics of participants receiving nirmatrelvir-ritonavir or azvudine before and after propensity-score matching

Basline characteristics	Before matching patients			After 1:1 propensity-score matching patients		
	Nirmatrelvir-ritonavir (n = 272)	Azvudine (n = 156)	P value[a]	Nirmatrelvir-ritonavir (n = 143)	Azvudine (n = 143)	P value[a]
Age, mean ± SD, yr	77.68 ± 13.42	76.67 ± 11.83	0.436	76.83 ± 13.47	76.45 ± 12.10	0.803
Sex, n (%)			0.150			0.716
Male	176 (64.71)	90 (57.69)		89 (62.24)	86 (60.14)	
Female	96 (35.29)	66 (42.31)		54 (37.76)	57 (39.86)	
BMI, mean ± SD[b,c]	22.99 ± 3.32	22.81 ± 2.99	0.576	22.82 ± 3.15	22.90 ± 3.05	0.829
Severity of COVID-19 before antivirals, n (%)			0.927			0.632
Mild to moderate	231 (84.93)	133 (85.26)		118 (82.52)	121 (84.62)	
Severe	41 (15.07)	23 (14.74)		25 (17.48)	22 (15.38)	
Smoking, n (%)	18 (6.62)	13 (8.33)	0.510	11 (7.69)	12 (8.39)	0.828
Drinking, n (%)	12 (4.41)	11 (7.05)	0.244	6 (4.20)	10 (6.99)	0.303
Diabetes, n (%)	62 (22.79)	46 (29.49)	0.125	42 (29.37)	39 (27.27)	0.694
Cardiovascular disease, n (%)	90 (33.09)	56 (35.90)	0.555	51 (35.66)	49 (34.27)	0.804
Chronic lung disease, n (%)	57 (20.96)	15 (9.62)	0.003	14 (9.79)	15 (10.49)	0.845
Tumor and immunosuppression, n (%)	84 (30.88)	24 (15.38)	< 0.001	27 (18.88)	24 (16.78)	0.643
LTM, median (IQR), × 10^9/L[b]	0.80 (0.50, 1.10)	1.00 (0.70, 1.30)	< 0.001	0.80 (0.60, 1.20)	1.00 (0.70, 1.30)	0.033
D-dimer, median (IQR), mg/L[b]	0.97 (0.56, 2.07)	0.88 (0.50, 1.56)	0.053	0.88 (0.50, 1.84)	0.87 (0.48, 1.56)	0.716
CRP, median (IQR), mg/L[b]	40.35 (14.18, 80.00)	20.90 (5.49, 58.58)	< 0.001	27.90 (10.62, 65.80)	24.10 (5.41, 64.90)	0.261

Abbreviations: *IQR* interquartile range, *LTM* lymphocyte count, *CRP* C-reactive protein, *BMI* body mass index
[a]P value was based on Student's t-test, the Mann–Whitney U test, χ^2 tests, or Fisher's exact test, as appropriate
[b]Missing data: 34 for BMI, 2 for LTM, 2 for D-dimer, and 4 for CRP
[c]BMI was calculated as weight in kilograms divided by height in meters squared

(± 12.86) years, with a majority (62.15%) being male. Age, sex, BMI, severity of COVID-19, smoking and drinking status, diabetes, and cardiovascular disease were not significantly different between the two groups. The proportions with chronic lung disease (20.96% vs.

9.62%, $P = 0.003$) and tumor and immunosuppression (30.88% vs. 15.38%, $P < 0.001$) appeared to be higher in the nirmatrelvir-ritonavir group compared to the azvudine group. Participants in the nirmatrelvir-ritonavir group exhibited significantly lower levels of LTM ($P < 0.001$) and higher levels of CRP ($P < 0.001$) compared to those in the azvudine group. The mean follow-up time for all patients was 27.84 days. After matching, we included 143 recipients of azvudine and 143 matched recipients of nirmatrelvir-ritonavir, resulting in balanced baseline characteristics between the two groups.

During the follow-up period, the incidence of all-cause mortality at day 28 was 5.51% in the nirmatrelvir-ritonavir group and 5.77% in the azvudine group. After adjusting for potential confounders in model 3, we observed no significant difference in all-cause 28-day mortality between the two groups. This suggests that azvudine may be noninferior to nirmatrelvir-ritonavir with respect to 28-day mortality (adjusted HR 1.41; 95% CI 0.56–3.56; $P = 0.471$), although there was a slightly lower mortality rate among nirmatrelvir-ritonavir recipients compared to those receiving azvudine (Table 2 and Fig. 2). The finding was consistent with the PSM analysis (crude HR 1.27; 95% CI 0.47–3.42; $P = 0.631$). Age (adjusted HR 1.06; 95% CI 1.01–1.11), BMI (adjusted HR 1.31; 95% CI 1.16–1.47), and severe illness type (adjusted HR 3.63; 95% CI 1.42–9.30) were identified as significant predictors of mortality in the study population (Supplementary Table S2).

Likewise, similar results were observed for secondary outcomes. During the 28-day follow-up period, the transfer rate to a critical condition was 6.99% in the nirmatrelvir-ritonavir group and 8.33% in the azvudine group, while P_{NANC} was 79.41% in the nirmatrelvir-ritonavir group and 84.62% in the azvudine group. The results regarding the risk of progression to a critical condition (adjusted HR 1.67; 95% CI 0.78–3.60; $P = 0.189$) and P_{NANC} (adjusted HR 0.87; 95%CI, 0.69–1.09; $P = 0.220$) within 28 days suggest that azvudine may be similarly effective in these outcomes as compared to nirmatrelvir-ritonavir, although there is a slight tendency for azvudine to perform slightly worse (Table 2 and Fig. 2). These results agree with those in the PSM analyses: risk of progression to a critical condition (crude HR 1.31; 95% CI 0.58–3.00; $P = 0.517$) and P_{NANC} (crude HR 0.83; 95% CI 0.64–1.07; $P = 0.146$). Meanwhile, age (adjusted HR 1.06; 95% CI 1.02–1.11), BMI (adjusted HR 1.18; 95% CI 1.06–1.31), and severity of COVID-19 (adjusted HR 4.58; 95% CI 2.05–10.24) were identified as potential risk factors for critical progression of COVID-19 (Supplementary Table S3), and a history of tumor and immunosuppression (adjusted HR 0.72; 95% CI 0.55–0.94) could be a risk factor for reduced P_{NANC} at day 28 (Supplementary Table S4).

Among the continuous outcomes, significant differences were observed in T_{FNANC}, with a significantly longer duration noted in the azvudine group as compared to the nirmatrelvir-ritonavir group (β 2.53; 95% CI 0.76–4.29; $P = 0.005$) (Table 2). There was no statistically significant difference in hospital stay duration between the azvudine and nirmatrelvir-ritonavir groups (β − 0.82; 95% CI − 2.78 to 1.15; $P = 0.414$). These were consistent with the PSM analysis results: T_{FNANC} (β 2.77; 95% CI 0.80–4.75; $P = 0.006$) and the length of hospital stay (β − 1.73; 95% CI − 3.98 to 052; $P = 0.133$). Additionally, a higher level of D-dimer was found to be associated with a longer T_{FNANC} (β 0.28; 95% CI 0.03–0.52) (Supplementary Table S5), while older individuals were observed to have prolonged hospital stays (β 0.13; 95% CI 0.05–0.21) (Supplementary Table S6). Despite comparable outcomes in most aspects, azvudine was found to be inferior to nirmatrelvir-ritonavir in terms of T_{FNANC}.

The results of the stratification and interaction analyses are presented in Supplementary Figs. S1–S5. The absence of a statistically significant interaction effect between azvudine and nirmatrelvir-ritonavir was demonstrated across all subgroups. In the subgroup analysis of the all-cause 28-day mortality and length of hospital stay outcomes, no significant differences were observed among any of the subgroups (Supplementary Figs. S1 and S5). In the subgroup analysis of the risk of progressing to a critical condition, as for participants "with tumor and immunosuppression", the azvudine

Table 2 Associations between antiviral use and efficacy outcomes in the regression analysis and propensity-score matching analysis

Analysis[a]	All-cause 28-day mortality		Risk of progressing to a critical condition within 28 days		Proportion with 28-day negative conversion of nucleic acid		Time to first nucleic-acid negative conversion[b]		Length of hospital stay[c]	
Regression analysis; values shown are no. of events/no. of patients at risk (%) or median (IQR), days										
Nirmatrelvir-ritonavir	15/272 (5.51)		19/272 (6.99)		216/272 (79.41)		15.00 (10.00, 21.00)		14.00 (9.00, 23.00)	
Azvudine	9/156 (5.77)		13/156 (8.33)		132/156 (84.62)		16.00 (12.00, 21.00)		15.00 (10.00, 20.00)	
Crude analysis, HR or β (95% CI) *P* value	1.03 (0.45–2.35)	0.943	1.19 (0.59–2.42)	0.624	0.93 (0.75–1.16)	0.516	1.89 (0.21–3.58)	0.029	− 1.46 (− 3.36 to 0.44)	0.134
Multivariable analysis: model 1[d], HR or β (95% CI) *P* value	1.26 (0.54–2.96)	0.590	1.42 (0.69–2.92)	0.337	0.93 (0.75–1.16)	0.524	2.06 (0.37–3.75)	0.018	− 1.23 (− 3.10 to 0.64)	0.197
Multivariable analysis: model 2[e], HR or β (95% CI) *P* value	1.21 (0.51–2.87)	0.659	1.42 (0.69–2.94)	0.341	0.88 (0.70–1.10)	0.252	2.39 (0.64–4.14)	0.008	− 0.89 (− 2.83 to 1.05)	0.371
Multivariable analysis: model 3[f], HR or β (95% CI) *P* value	1.41 (0.56–3.56)	0.471	1.67 (0.78–3.60)	0.189	0.87 (0.69–1.09)	0.220	2.53 (0.76–4.29)	0.005	− 0.82 (− 2.78 to 1.15)	0.414
Propensity-score matching analysis; values shown are no. of events/no. of patients at risk (%) or median (IQR), days										
Nirmatrelvir-ritonavir	7/143 (4.90)		10/143 (6.99)		120/143 (83.92)		13.00 (10.00, 19.00)		15.00 (9.00, 23.00)	
Azvudine	9/143 (6.29)		13/143 (9.09)		121/143 (84.62)		16.50 (12.00, 21.25)		15.00 (10.00, 20.00)	
Crude PSM analysis, HR or β (95% CI) *P* value	1.27 (0.47–3.42)	0.631	1.31 (0.58–3.00)	0.517	0.83 (0.64–1.07)	0.146	2.77 (0.80–4.75)	0.006	− 1.73 (− 3.98 to 0.52)	0.133

Abbreviations: *HR* hazard ratio, *IQR* interquartile range, *PSM* propensity-score matching

[a]Was measured by azvudine vs. nirmatrelvir-ritonavir

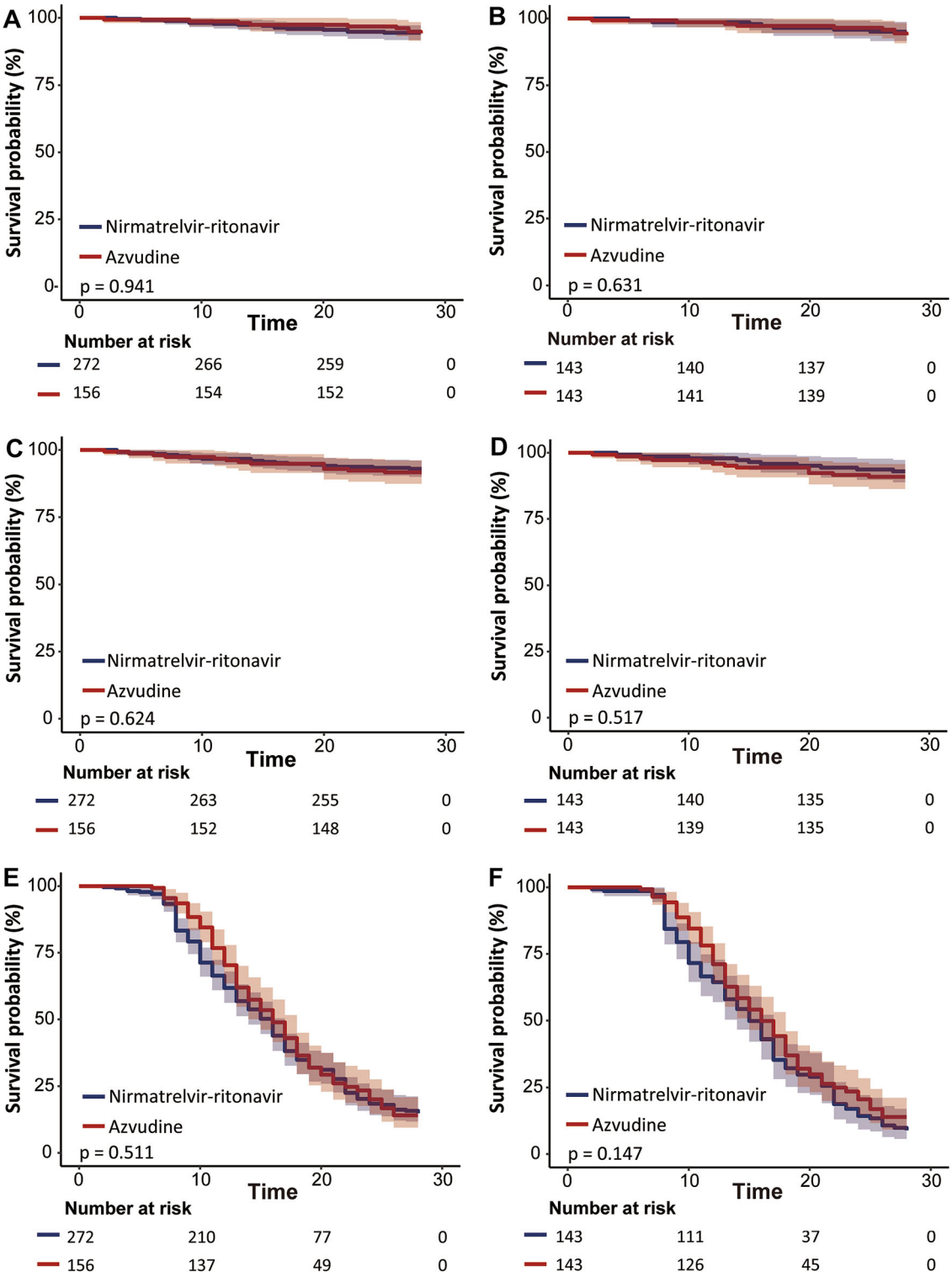
[b]Patients who died or were lost before the nucleic acid turned negative were excluded

[c]Patients who died during hospitalization were excluded

[d]Model 1 was adjusted for age, sex, BMI, and severity of COVID-19

[e]Model 2 was adjusted as for model 1 plus diabetes, cardiovascular diseases, chronic lung disease, and tumor and immunosuppression

[f]Model 3 was adjusted as for model 2 plus LTM, D-dimer, and CRP


A
Survival probability (%)
100
75
50
25
0
Nirmatrelvir-ritonavir
Azvudine
p = 0.941
0
10
20
30
Time
Number at risk
272 266 259 0
156 154 152 0
B
Survival probability (%)
Nirmatrelvir-ritonavir
Azvudine
p = 0.631
Time
Number at risk
143 140 137 0
143 141 139 0
C
Survival probability (%)
Nirmatrelvir-ritonavir
Azvudine
p = 0.624
Time
Number at risk
272 263 255 0
156 152 148 0
D
Survival probability (%)
Nirmatrelvir-ritonavir
Azvudine
p = 0.517
Time
Number at risk
143 140 135 0
143 139 135 0
E
Survival probability (%)
Nirmatrelvir-ritonavir
Azvudine
p = 0.511
Time
Number at risk
272 210 77 0
156 137 49 0
F
Survival probability (%)
Nirmatrelvir-ritonavir
Azvudine
p = 0.147
Time
Number at risk
143 111 37 0
143 126 45 0

◀**Fig. 2** Kaplan–Meier charts of all-cause 28-day mortality for the main cohort (**A**) and the PSM cohort (**B**), risk of progressing to a critical condition for the main cohort (**C**) and the PSM cohort (**D**), and T_{FNANC} for the main cohort (**E**) and the PSM cohort (**F**) of azvudine recipients versus nirmatrelvir-ritonavir recipients. *PSM* propensity-score matching; T_{FNANC} time to first nucleic-acid negative conversion

group showed a significantly higher risk than nirmatrelvir-ritonavir group (adjusted HR 4.39; 95% CI 1.34–14.41, P = 0.021); on the other hand, for participants "without tumor and immunosuppression", the risk in azvudine and nirmatrelvir-ritonavir group showed no significant difference (P = 0.445) (Supplementary Fig. S2). In the "severe" subgroup, the azvudine group showed a significantly lower P_{NANC} compared to the nirmatrelvir-ritonavir group (adjusted HR 0.43; 95% CI 0.19–0.95, P = 0.038); while in the "mild-to-moderate" subgroup, there was no significant difference in P_{NANC} between the azvudine and nirmatrelvir-ritonavir groups (P = 0.609) (Supplementary Fig. S3). A significantly longer T_{FNANC} was observed in the azvudine group compared to the nirmatrelvir-ritonavir group in all of the age and BMI subgroups. The differences were particularly pronounced in "younger" (β 4.87; 95% CI 0.19–9.55; P = 0.047) or "obese" (β 3.55; 95% CI 0.42–6.69; P = 0.028) subgroups (Supplementary Fig. S4). We also observed that T_{FNANC} was significantly longer in the "male" (β 3.24; 95% CI 0.83–5.66; P = 0.009), "severe ill type" (β 6.38; 95% CI 1.46–11.29; P = 0.015), "non-smoking" (β 2.50; 95% CI 0.69–4.31; P = 0.007), "non-drinking" (β 2.41; 95% CI 0.60–4.23; P = 0.009), "without diabetes" (β 1.89; 95% CI 0.02–3.76; P = 0.049), "with cardiovascular disease" (β 3.76; 95% CI 0.38–7.14; P = 0.031), and "without tumor and immunosuppression" (β 2.68; 95% CI 0.78–4.59; P = 0.006) subgroups by comparing azvudine and nirmatrelvir-ritonavir (Supplementary Fig. S4).

The results of sensitivity analyses are presented in Table 2 and Supplementary Tables S7–S8. Consistent findings were obtained from multilevel regression models (Table 2) and complete data analyses with missing values excluded (Supplementary Tables S7 and S8), indicating the robustness and stability of the results.

After 28 days of follow-up, similar incidences of adverse events were observed in the nirmatrelvir-ritonavir and azvudine groups (4.41% vs. 3.21%, P = 0.538) (Table 3). Among patients who received nirmatrelvir-ritonavir, the most common adverse events were elevated liver enzymes (1.84%), followed by gastrointestinal disorders (1.10%) and skin rash (0.74%). Other adverse effects included dizziness, weakness, shortness of breath, sweating, and dry throat (all 0.37%). Similarly, the adverse effects observed during azvudine therapy were gastrointestinal disorders (1.92%), elevated liver enzymes (1.28%) and skin rash (0.64%).

DISCUSSION

This study investigated the efficacy and safety profiles of azvudine and nirmatrelvir-ritonavir in a representative cohort of 428 hospitalized adult patients with COVID-19 in China with a follow-up period exceeding 28 days. Results showed that initiation of azvudine was potentially non-inferior to nirmatrelvir-ritonavir in 28-day mortality, risk of progression to a critical condition, P_{NANC}, length of hospital stay, and the incidence of adverse reactions, whereas nirmatrelvir-ritonavir demonstrated a superior T_{FNANC} compared to azvudine. In summary, the results indicate that azvudine may exhibit comparable efficacy and safety to nirmatrelvir-ritonavir in certain outcomes among hospitalized adult patients with COVID-19 in China.

To date, only two studies have compared azvudine with nirmatrelvir-ritonavir, and those studies focused solely on viral load dynamics or clinical efficacy outcomes [26, 27]. Our study revealed that the azvudine group exhibited a prolonged T_{FNANC} compared to the nirmatrelvir-ritonavir group, which is consistent with previous studies that focused on viral load dynamics outcomes [26]. In addition, our investigation found that azvudine and nirmatrelvir-ritonavir had comparable efficacy profiles, although the latter showed slightly better all-cause mortality, risk of progression to a

Table 3 Incidences of adverse events in the study participants

Adverse event category	Nirmatrelvir-ritonavir (n = 272)	Azvudine (n = 156)	P value
Any adverse event	12 (4.41%)	5 (3.21%)	0.538
More than one adverse event	3 (1.10%)	1 (0.64%)	
Serious adverse event[a]	1 (0.37%)	0 (0.00%)	
Gastrointestinal disorders[b]	3 (1.10%)	3 (1.92%)	
Elevated liver enzymes	5 (1.84%)	2 (1.28%)	
Skin rash	2 (0.74%)	1 (0.64%)	
Dizziness	1 (0.37%)	0 (0.00%)	
Weakness	1 (0.37%)	0 (0.00%)	
Shortness of breath	1 (0.37%)	0 (0.00%)	
Sweating	1 (0.37%)	0 (0.00%)	
Dry throat	1 (0.37%)	0 (0.00%)	

[a]Severe adverse effects were defined as grade 3–5 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0
[b]Including nausea, diarrhea, abdominal distension, dyspepsia

critical condition, and P_{NANC}. The results of our study regarding all-cause mortality and risk of progression to a critical condition are not entirely consistent with previous studies, which showed that the azvudine groups had a significantly lower incidence rate of composite disease progression and tended towards a nonsignificantly reduced all-cause mortality rate compared to the nirmatrelvir-ritonavir groups [27]. This inconsistency in results may be attributed to differences in the study population, outcome measures, or follow-up time. Firstly, our study was conducted in hospitalized patients with COVID-19 in Zhejiang Province of China from December 20, 2022 to January 31, 2023, while the prior research was carried out in Hunan Province during the period from December 5, 2022 to January 31, 2023, so the study population was slightly different. Secondly, the risk of progression to a critical condition outcome in our study was defined as individuals who experience respiratory failure requiring mechanical ventilation, develop shock, or suffer from multiple organ failures necessitating treatment in the ICU (Supplementary Table S1), while the incidence rate of composite disease progression in the prior study was a composite disease progression outcome that included all-cause death, intensive care unit admission, initiation of invasive mechanical ventilation, and need for high-flow oxygen therapy. Thirdly, we performed a 28-day follow-up for the two outcomes, whereas the previous study had a follow-up time of 38 days. Nevertheless, the results of our study provide interesting and controversial findings regarding the clinical efficacy of azvudine and nirmatrelvir-ritonavir.

Furthermore, our study directly compared the safety of azvudine and nirmatrelvir-ritonavir in hospitalized adult patients with COVID-19, which has not been documented in previous research. The present analysis did not reveal any noteworthy variation in the incidence of adverse events among these groups, aligning with prior phase 2–3 investigations involving azvudine [21, 22] or nirmatrelvir-ritonavir [8] compared to their controls. Therefore, our findings suggest that both azvudine and nirmatrelvir-ritonavir are safe therapeutic options recommended by the guidelines [28].

Meanwhile, there are several noteworthy observations from subgroup analyses. Nirmatrelvir-ritonavir demonstrated superiority over azvudine in subgroups characterized by a male gender, severe illness status, non-smoking and non-drinking habits, cardiovascular disease or a history of tumor and immunosuppression with respect to outcomes such as the risk of progression to a critical condition, P_{NANC} and T_{FNANC}. The findings suggest that nirmatrelvir-ritonavir may confer advantages over azvudine in specific populations, which is a controversial and different result compared to what was found in the previous study [27]. Hence, more studies are needed to verify these results.

We also included patients with severe illness in order to provide an opportunity for those who developed severe disease within 5 days of onset to receive treatment. A previous multicenter randomized controlled trial was conducted to evaluate the efficacy and safety of nirmatrelvir-ritonavir in the treatment of adult patients with severe disease [29]. Therefore, we can gather valuable insights into patients' preferences for antiviral therapy based on the severity of COVID-19.

A strength of this study lies in the utilization of a real-world hospitalized cohort, with data collection facilitated through an electronic medical record system. This approach enables close monitoring and documentation of clinical details, as well as systematic coverage of clinical outcomes. Another strength is our adjustment for potential confounding covariates in multiple models, as well as the performance of various analyses, including regression analysis, PSM analysis, subgroup analysis and sensitivity analysis, based on previous literature [30, 31]. This makes our findings more robust. One additional strength is that we systematically evaluated six clinical outcomes in hospitalized adult patients with COVID-19, including the safety outcomes, which are the most comprehensive outcome measures to date. However, several limitations need to be addressed. Firstly, this was a single-center study with participants only from China. Thus, the findings may not fully generalize to other countries, and further validation is required in wider geographic regions. Secondly, although we included consecutive cases, considered many confounders, and performed multiple analyses in this study, residual confounding and unmeasured confounders between the two groups remain a concern in a retrospective study. Thirdly, clinicians may prefer azvudine over nirmatrelvir-ritonavir for treating patients on multiple medications due to contraindications related to drug–drug interactions. Hence, we excluded patients with drug-related contraindications and those with severe renal or liver disorders to allow for a fair comparison between the two groups. Fourthly, it is noteworthy that although the discharge criteria protocols for patients with COVID-19 used by different consultants were similar, there may still have been some subtle differences resulting in slightly different lengths of hospital stay. Thus, generalization of the results of our length of hospital stay outcome to other healthcare settings should be carried out with caution. Finally, the sample size of azvudine may not be large enough due to the rigorous study design and the strict inclusion and exclusion criteria for patient enrollment. Also, our subgroup analyses may have been underpowered due to their relatively small sample sizes in certain patient subgroups. Further research with larger sample sizes is greatly needed in the future.

CONCLUSION

In conclusion, this retrospective cohort study of hospitalized patients with COVID-19 showed that azvudine probably possessed comparable efficacy and safety to nirmatrelvir-ritonavir, although it was less effective than nirmatrelvir-ritonavir in some outcomes. Our research supplements existing studies and provides additional evidence for the real-world comparison between azvudine and nirmatrelvir-ritonavir. Meanwhile, these results will help physicians reconsider the selection and prioritization of antiviral drugs. Larger sample sizes or multicenter clinical studies are warranted for further investigation.

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Disclosures. The authors Qinqin Zhao, Bei Zheng, Bing Han, Pinpin Feng, Zhongni Xia, Hong Jiang, Yin Ying, Jun Zhu, Cheng Fei, Junlei Xiang, Lingli Shen, Qiliang Luo, Yinhuan Wu, Ayiguzhali Wusiman, Chuanwei Xin, Meiling Zhang, Gonghua Li and Xiang Li have nothing to disclose.

Compliance with Ethics Guidelines. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tongde Hospital in Zhejiang Province (acceptance number: 2023–015(K)). The study was exempted from the need for informed consent from patients due to its retrospective nature.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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