Effectiveness and Optimal Timing of Azvudine in COVID-19 Patients: A Multi-center Retrospective Study in Beijing, China

Xinjie Han
The 8 th Medical Center, Chinese PLA General Hospital
Xiaobo Han
The 8 th Medical Center, Chinese PLA General Hospital
Yongqian Wang
Peking University First Hospital
Ze Wang
Chinese PLA Medical School
Junchang Cui
The 8 th Medical Center, Chinese PLA General Hospital
Weiguo Zhao
The 8 th Medical Center, Chinese PLA General Hospital
Guoxin Mo
The 8 th Medical Center, Chinese PLA General Hospital
Yuhong Liu
The 8 th Medical Center, Chinese PLA General Hospital
Mengli Zheng
The 8 th Medical Center, Chinese PLA General Hospital
Fei Xie
First Affiliated Hospital of Chinese PLA General Hospital
Kaifei Wang
First Affiliated Hospital of Chinese PLA General Hospital
Jiguang Meng
Forth Affiliated Hospital of Chinese PLA General Hospital
Xin Yuan
Fifth Affiliated Hospital of Chinese PLA General Hospital
Zhihai Han
Sixth Affiliated Hospital of Chinese PLA General Hospital
Kun Xiao
The 8 th Medical Center, Chinese PLA General Hospital
Pan Pan

The 8 th Medical Center, Chinese PLA General Hospital

Junping Sun

The 8 th Medical Center, Chinese PLA General Hospital

Mingyue Zhang

First Affiliated Hospital of Chinese PLA General Hospital

Xinxin Zhang

The 8 th Medical Center, Chinese PLA General Hospital

Haibo Cheng

Shandong Future Network Research Institute, Jiangsu Future Network Group Co., Ltd

Wuxiang Xie

Peking University First Hospital

Lixin Xie (xielx301@126.com)

The 8 th Medical Center, Chinese PLA General Hospital

Research Article

Keywords: COVID-19, Azvudine, multi-center, all-cause mortality, clinical improvement

Posted Date: July 14th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3145554/v1

Additional Declarations: No competing interests reported.

Abstract

Background: Clinical effectiveness of Azvudine against coronavirus infection and optimal time for initiation of Azvudine treatment to hospitalized COVID-19 patients are not fully understood.

Methods: This is a multi-center retrospective cohort study, and five clinical centers of the Chinese People's Liberation Army General Hospital participated. From omicron pandemics, 6218 hospitalized patients confirmed with COVID-19 from December 10, 2022, to February 20, 2023, were retrieved for this study. After exclusions and propensity score matching , 428 Azvudine recipients and 428 controls were included with a follow-up of 28 days. The primary outcome was all-cause mortality during 28 days of hospitalization, and the secondary outcome was the proportion of patients with clinical improvement up to day 28.

Results: The Azvudine group had a lower crude all-cause death rate when compared to the control group (2.82 per 1000 person-days vs. 4.52 per 1000 person-days; HR: 0.63, 95%CI: 0.40-1.00; *P*=0.038). Notably, the incidence rate of clinical improvement outcome was significantly higher in patients who received Azvudine within 5 days from the onset of symptoms, compared to the control group (Median days: 9 vs. 10; *P*=0.007). Subgroup analyses showed that chronic lung disease and corticosteroid treatment acted as protective factors *(P*=0.010; *P*=0.050).

Conclusions: Clinical effectiveness of Azvudine in improving all-cause mortality in COVID-19 patients was seen, and initiation of Azvudine treatment within 5 days of the onset of symptoms was found to be significant. Additionally, the findings revealed the protective effect of Azvudine in COVID-19 patients with chronic lung disease.

Introduction

With the continuous spread of coronavirus and the emergence of infection with new variants worldwide, the health care system is overburdened, impacting the global economy. The invention of therapeutics for coronavirus disease 2019 (COVID-19) has been in progress. Azvudine, also known as FNC (2'-deoxy-2'-β-fluoro-4'-azidocytidine), is a novel nucleoside reverse transcriptase inhibitor that has been proven to possess antiviral effects against multiple viruses, such as HIV, HBV, HCV, and EV [1], and is now widely used in COVID-19 treatment.

A previous randomized clinical trial performed in moderately affected COVID-19 patients showed that Azvudine can accelerated the elimination of coronavirus, decreased the viral load significantly, and shortened the time of nucleic acid to become negative, compared to the placebo group (Trial registration number: NCT04668235) [2]. Similar conclusions were drawn in mild and severe COVID-19 cases by subsequent studies [3]. In a single-center retrospective cohort study that analyzed 2118 hospitalized patients from Xiangya Hospital in Changsha, Hunan province, Azvudine treatment resulted in a lower rate of composite disease progression of COVID-19 in patients with pre-existing conditions, but had no significant difference in all-cause death, compared to the control group [4]. Azvudine has been commonly

recommended for COVID-19 patients in the Chinese Diagnosis and Treatment Protocol for COVID-19 (trial version 10) [5], but the time of initiating Azvudine administration has not yet been recommended [1, 5]. To the best of our knowledge, current studies mainly focus on the efficacy of Azivudine on nucleic acid conversion time and symptom's improvement [2]. There has been no retrospective cohort study that elucidate the optimal initiation time of Azvudine administration .

Given the scarcity of real-world research data, this multi-center retrospective cohort study aimed to verify the efficacy and safety of Azvudine treatment for COVID-19 during the period of the Omicorn pandemic, and to identify the optimal initiation time for Azvudine treatment.

Methods

Study design and patientss' characteristics

The data for this multi-center, retrospective cohort study was retrieved from five clinical centers of the Chinese People's Liberation Army General Hospital, which is the largest military hospital in China.

All patients confirmed with COVID-19 according to the diagnostic criteria of the Chinese Diagnosis and Treatment Protocol for COVID-19 (trial version 10) between December 10, 2022, and February 20, 2023, from five participating centers were included in the analysis. The exclusion criteria were as follows. (1) Patients who were under 18 years old; (2) Patients who had more than 2 days from admission to treatment; (3) Patients with hospitalization duration of less than 24 hours; (4) Patients who did not received Azvudine or combination of Azvudine with other antiviral drugs; (5) Patients who were pregnant.

This research was approved by the Ethics Committee of People's Liberation Army General Hospital (NO. 309202302230712). Informed consent was not required due to the retrospective nature of the study design.

Data collection

The demographic and baseline clinical characteristics of all eligible patients, including age, sex, time from the onset of symptoms to admission, previous comorbidities, CCI (Charlson Comorbidity Index), eGFR at admission, concomitant treatment, respiratory support at admission, and laboratory testing were extracted from the electronic health records.

Treatment exposure

Treatment exposure was defined as receipt of Azvudine treatment. All Azvudine recipients were treated with oral Azvudine tablets 5 mg daily, for up to 14 days, as recommended in the medication manual. Patients were observed from the admission date until the occurrence of outcome events up to day 28, whichever occurred first.

Outcomes and definitions

The primary outcome was all-cause death by day 28, and the secondary outcome was the proportion of participants who showed clinical improvement through day 28.

To assess the clinical improvement, all enrolled patients were evaluated with a baseline score based on the WHO clinical improvement ordinal scale at admission and reevaluated daily until day 28 or death, whichever occurred first. The criterion of clinical improvement was a decrease in score based on the WHO clinical improvement ordinal scale (on a scale of 0 to 8, with higher scores indicating greater severity) with at least two points compared with the baseline score.

To assess drug adverse events, new onset of liver and kidney dysfunction was considered. New liver function impairment was defined as an increase of ALT(alanine aminotransferase) or AST(aspartate aminotransferase) above 200 U/L. New onset renal impairment was defined as eGFR of < 30mL/min/1.73 m^2 compared with eGFR of ≥ 30mL/min/1.73 m^2 at admission.

Covariates

Baseline covariates of all enrolled patients were age, CCI, clinical improvement score at baseline, corticosteroids treatment, malignant tumor, liver disease, diabetes mellitus, chronic renal disease, nucleic acid positive, time from the onset of symptoms to admission, eGFR, primary diagnosis of COVID-19, solid organ transplant, hypertension, coronary heart disease, cerebrovascular disease, Alzheimer's disease, and tocilizumab treatment.

Statistical analysis

Numbers and percentages were used to describe categorical variables. Mean ± standard deviation (SD) or the median with the interquartile range (IQR) was used to describe continuous variables. Student’ s t-test, Wilcoxon rank test, or chi-square test was used to test the differences in baseline characteristics.

Propensity score matching (PSM) (1:1) was used to match the Azvudine group and the control group to reduce the confounding bias of potential risk factors. The two groups were adjusted for covariates including age, CCI, clinical improvement score at baseline, corticosteroids treatment, malignant tumor, liver disease, diabetes mellitus, chronic renal disease, nucleic acid positive, time from the onset of symptoms to admission, eGFR, primary diagnosis of COVID-19, solid organ transplant, hypertension, coronary heart disease, cerebrovascular disease, Alzheimer's disease, and tocilizumab treatment, which were selected based on professional knowledge and information from previous studies.

The caliper’s matching algorithm was used without replacement, which was designed with a caliper value of 0.2 for the matching procedure. Love plot showing absolute standardized mean differences (ASMD) evaluated the covariates balance before and after PSM, with a threshold of 0.1 which was applied for determining imbalance [6]. All analysis was performed on the matched sample.

The primary analysis was to assessed the associations between Azvudine treatment and all-cause death within 28 days of hospital admission. A cumulative incidence of study outcome was calculated based on the Kaplan-Meier estimator, using the Log-rank test applied for inference. The crude incidence rate per

1000 person-days of outcomes was also calculated. The Cox proportional hazard regression was used to estimated the hazard ratio (HR) and 95% confidence intervals (CI) associated with the treatment exposure. A frailty term was added to the Cox models to account for heterogeneity between study centers [7].

We also performed sensitivity analyses. First, we performed stratified analysis based on the duration from the onset of symptoms to treatment initiation (≤ 5 days; > 5 days). Second, we performed subgroup analyses based on selected baseline characteristics, with the application of the Z test for detecting interactions. Third, we compared drug adverse events between groups, with the use of the Wald method to calculate risk ratio (RR). Finally, the days to the occurrence of study outcomes were compared between groups, in addition to modeling the hazard function of study outcomes and estimating the HR.

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc,Cary, NC, USA) and R language version 3.6.2 (R Foundation, Vienna, Austria), with a two-tailed alpha of 0.05 referred to as a statistically significant level.

Results

Characteristics of patients

A total of 6218 hospitalized patients confirmed with COVID-2019 during the Omicron pandemic period were considered for this study. Of these patients, 2287 were excluded due to the exclusion criteria. Finially, 428 Azvudine recipients and 428 controls were included in the analyses after propensity score matching to verify the efficacy and safety of Azvudine treatment for COVID-19 (Fig. 1).

Propensity score matching accounted for age, CCI, clinical improvement score at baseline, corticosteroids treatment, malignant tumo, liver disease, diabetes mellitus, chronic renal disease, nucleic acid positive, time from the onset of symptoms to admission, eGFR, primary diagnosis of COVID-19, solid organ transplant, hypertension, coronary heart disease, cerebrovascular disease, Alzheimer's disease, and tocilizumab treatment (Supplementary Fig. S1).Table 1 shows the demographics and clinical characteristics of the Azvudine and control groups before and after 1:1 propensity score matching (Supplementary table S1).

All-cause death and clinical improvement outcomes

After propensity score matching, the crude all-cause death rate was 2.82 per 1000 person-days in patients who received Azvudine compared to 4.52 per 1000 person-days in the control group (P<0.05).The crude incidence rate of clinical improvement outcome was 57.83 per 1000 person-days in Azvudine group and 52.06 per 1000 person-days in control group with no statistical difference between the two groups (Median days: 12 vs. 11; P>0.05) (Fig. 2, Table 2).

Sensitivity analyses

Upon subgroup analyses, the all-cause death rate was lower in patients who received Azvudine within 5 days from the onset of symptoms compared to the control group (P<0.05) (Fig. 3). Notably, the incidence rate of clinical improvement outcome was significantly higher in patients who received Azvudine within 5 days from the onset of symptoms compared with the control group (Median days: 9 vs. 10; P<0.01) (Fig. 3). The incidence rate of all-cause death and clinical improvement in patients who received Azvudine more than 5 days from the onset of symptoms did not differ from the control group (P>0.05) (Supplementary Fig. S2).

Further, the subgroup analysis did not find any other interaction factors except for identifying chronic lung disease and corticosteroid treatment as protective factors*(*P<0.05; P = 0.05). The subgroup analysis did not show any significant results for all-cause death (Fig. 4).

Adverse events

The incidence of new onset of liver impairment in the Azvudine group was lower than in the control group (2.6% vs. 6.1%; P<0.05), the incidence of new kidney impairment between the two groups did not differ significantly (2.3% vs. 4.4%, P>0.05) (Supplementary Table S2).

Discussion

In this multi-center retrospective cohort study that analyzed hospitalized COVID-19 patients, Azvudine treatment resulted in a lower rate of all-cause death compared to the control group. In the subgroup analyses, patients who received Azvudine within 5 days from the onset of symptoms showed a significantly higher clinical improvement rate compared to the control group, which was consistent with the outcome of the survival rate. To the best of our knowledge, this was the first multi-center retrospective cohort study that highlighted the significance of initiation of Azvudine treatment within 5 days of the onset of symptoms for COVID-19. This retrospective analysis provided real-world evidence for the optimal initiation time of Azvudine treatment.

As the first launched Chinese oral anti-COVID-19 drug [8], Azvudine exhibited antiviral activity effectively against coronavirus in preliminary clinical trials [2, 4, 9, 10, 11]. Meanwhile, several retrospective cohort studies suggested that Azvudine showed more effectiveness in hospitalized COVID-19 patients compared with Nirmatrelvir-ritonavir and Paxlovid in terms of composite disease progression outcome [12, 13]. In this retrospective analysis, the crude all-cause death rate was 2.82 per 1000 person-days in patients who received Azvudine vs. 4.52 per 1000 person-days in the control group, suggesting that Azvudine administration caused a lower mortality rate. Consistently, a previous single-center retrospective cohort study conducted in Xiangya Hospital founded that Azvudine treatment was associated with a reduced risk of composite disease progression and all-cause mortality in COVID-19 patients [4].

Notably, this retrospective study found that the rate of clinical improvement outcome was significantly higher in patients who received Azvudine within 5 days from the onset of symptoms compared with the control group ($P<0.05$). Moreover, this protective effect was more pronounced in patients with chronic lung disease and patients received corticosteroid treatment simultaneously. However, initiating Azvudine administration after five days of the onset of symptoms did not have statistically significant clinical improvement. The reason for no difference in the overall clinical improvement rate might have been that the majority of the Azvudine recipients initiated Azvudine treatment after five days from the onset of symptoms in the two groups. Therefore, the findings suggested that early administration of Azvudine in clinical practice can better improve clinical outcomes. Nevertheless, more real-world studies are needed to substantiate this conclusion.

Previous studies found that males, aged over 65 with smoking habit and comorbidities were at high-risk of developing into the critical or mortal conditions [14, 15, 16]. Thus, the current subgroup analyses included diverse factors such as age, sex, previous comorbidities, concomitant treatment, and respiratory support at admission. Some previous studies showed that Azvudine provided better protection in male and elderly patients [4, 9]. A previous study conducted in Shanghai found that Azvudine improved 60-day mortality among severely and critically ill patients with COVID-19 who received one or more therapeutic interventions [17]. This current subgroup analysis found the simultaneous administration of corticosteroids with Azvudine as a protective factor. Additionally, the subgroup analyses showed that Azvudine treatment significantly benefited COVID-19 patients with chronic lung disease in clinical improvement. Patients with chronic lung disease may have been more vulnerable to coronavirus and may have initiated cytokine storm and had more pulmonary complications after being infected with the coronavirus [18]. However, deciphering the potential mechanism requires more investigations.

This retrospective study also focused on some vulnerable populations such as solid organ transplant recipients and immunocompromised patients (including hematological cancers and other malignant tumors). Previous studies found that antiviral drugs can accelerated the virus clearance and improved the prognosis on solid organ transplant recipients and patients undergoing hemodialysis with COVID-19 [19, 20]. Perhaps due to the small number of patients analyzed, the study results did not show that Azvudine had a protective effect in organ transplant recipients or immunocompromised patients.

Azvudine has shown desirable pharmacokinetic properties, with excellent efficacy and safety, in its initial clinical trials (NCT04303598, CXHS2000016, CXHS2000017) [21]. In this study, the rate of new onset of liver impairment in the Azvudine group was lower than in control group, and the incidence of new kidney impairment did not differ significantly between the two groups. However, due to the small number of adverse events, we did not evaluate the potential drug-to-drug interactions. Thus, larger sample size studies are needed to assess the safety of Azvudine in real-world situation.

The advantages of this retrospective study were multi-center data and a considerable sample size design. Further diverse COVID-19 patients were included, including patients with previous comorbidities, patients who needed oxygen support at admission or not, and solid organ transplant patients, which made the

findings more credible and closer to the real-world situation. Nevertheless, there were still some limitations in this study. First, due to the change of medical policy at that time, not all patients were tested for nucleic acid during the follow-up, and therefore, we did not analyze the changes in nucleic acid CT values. Second, there might have been still unadjusted confounding variables related to the disease severity. Third, recent studies have showed that antiviral treatment in vaccinated COVID-19 patients reduced the risk of hospitalization or progression [22, 23]. Due to the limited clinical data, it was unclear whether the vaccine status had an impact on this study's findings.

In conclusion, this study's findings confirmed the clinical effectiveness of Azvudine in improving all-cause mortality of COVID-19 patients, and highlighted the significance of initiation of Azvudine treatment within 5 days of the onset of symptoms. Additionally, this study revealed the protective effect of Azivudine on patients with chronic lung disease.

Declarations

Acknowledgments

We are grateful to all co-workers working on the front line during the pandemic period. We appreciate all participants and their families involved in this study and thank the statisticians from the Peking University Clinical Research Institute, Peking University First Hospital,who guided this study design and analyses.

Ethical Approval

This research was approved by the Ethics Committee of People's Liberation Army General Hospital (NO. 309202302230712). Informed consent was not required due to the retrospective nature of the study design.

Competing interests

All authors in this study declare no competing conflicts.

Authors' contributions

Han Xinjie, Han Xiaobo, WY, WZ, XW and XL reviewed the literature, designed statistical analysis, conducted analyses, wrote the manuscript; CJ, ZW, MG, LY, Zheng Mengli, XF, WK, MJ, YX, HZ, and CH collected and analyzed clinical data, also contributed to the interpretation of the analysis; XK, PP, SJ, Zhang Mingyue and ZX prepared some paragraphs of the manuscript. All authors contributed to the interpretation of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding

This retrospective study was supported by China National Nature Science Foundation (82172109).

Availability of data and materials

Not applicable.

References

1. Xu N, Yang J, Zheng B et al. The Pyrimidine Analog FNC Potently Inhibits the Replication of Multiple Enteroviruses. J Virol 2020 Apr 16;94(9):e00204–20. doi: 10.1128/JVI.00204-20. PMID: 32075935; PMCID: PMC7163137.
2. Da Silva RM, Gebe Abreu Cabral P, De Souza SB et al. Serial viral load analysis by DDPCR to evaluate FNC efficacy and safety in the treatment of mild cases of COVID-19. Front Med (Lausanne). 2023 Mar 14;10:1143485. doi:10.3389/fmed.2023.1143485. PMID: 37007788; PMCID: PMC10053779.
3. Ren Z, Luo H, Yu Z, Randomized A, et al. Open-Label, Controlled Clinical Trial of Azvudine Tablets in the Treatment of Mild and Common COVID-19, a Pilot Study. Adv Sci (Weinh). 2020 Oct;7(19):e2001435. 10.1002/advs.202001435. Epub 2020 Aug 13. PMID: 35403380; PMCID: PMC7404576.
4. 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 Apr;95(4):e28756. doi: 10.1002/jmv.28756. PMID: 37185838.
5. General Office of the National Health Commission. Notice on the issuance of Diagnosis and Treatment Protocol for novel coronavirus infection (trial version 10). (2023).
6. Chan KC, Yam SC, Zhang Z. Globally efficient non-parametric inference of average treatment effects by empirical balancing calibration weighting. J R Stat Soc Series B Stat Methodol. 2016 Jun;78(3):673–700. doi: 10.1111/rssb.12129. Epub 2015 Nov 8. PMID: 27346982; PMCID: PMC4915747.
7. Therneau T, Grambsch P, Pankratz VS. Penalized survival models and frailty. J Comput Graphical Stat. 2003;12:156–75.
8. Yu B, Chang J. The first Chinese oral anti-COVID-19 drug Azvudine launched. Innovation (Camb). 2022 Nov 8;3(6):100321. doi: 10.1016/j.xinn.2022.100321. Epub 2022 Sep 9. PMID: 36106026; PMCID: PMC9461232.
9. Sun Y, Jin L, Dian Y et al. Oral Azvudine for hospitalised patients with COVID-19 and pre-existing conditions: a retrospective cohort study. EClinicalMedicine. 2023 May 5;59:101981. doi: 10.1016/j.eclinm.2023.101981. PMID: 37193346; PMCID: PMC10167478.
10. Najjar-Debbiny R, Gronich N, Weber G et al. Effectiveness of Paxlovid in Reducing Severe Coronavirus Disease 2019 and Mortality in High-Risk Patients. Clin Infect Dis. 2023 Feb 8;76(3):e342-e349. doi: 10.1093/cid/ciac443. Erratum in: Clin Infect Dis. 2023 Mar 21;76(6):1158–1159. PMID: 35653428; PMCID: PMC9214014.

11. Ren Z, Luo H, Yu Z, Randomized A, et al. Open-Label, Controlled Clinical Trial of Azvudine Tablets in the Treatment of Mild and Common COVID-19, a Pilot Study. Adv Sci (Weinh). 2020 Oct;7(19):e2001435. 10.1002/advs.202001435. Epub 2020 Aug 13. PMID: 35403380; PMCID: PMC7404576.
12. 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 Apr;95(4):e28756. doi: 10.1002/jmv.28756. PMID: 37185838.
13. Dian Y, Meng Y, Sun Y et al. Azvudine versus Paxlovid for oral treatment of COVID-19 in Chinese patients with pre-existing comorbidities. J Infect. 2023 May 17:S0163-4453(23)00290-6. doi: 10.1016/j.jinf.2023.05.012. Epub ahead of print. PMID: 37207823; PMCID: PMC10188372.
14. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020 Aug;81(2):e16–e25. 10.1016/j.jinf.2020.04.021. Epub 2020 Apr 23. PMID: 32335169; PMCID: PMC7177098.
15. Gal-Oz ST, Maier B, Yoshida H et al. ImmGen report: sexual dimorphism in the immune system transcriptome. Nat Commun 2019 Sep 20;10(1):4295. doi: 10.1038/s41467-019-12348-6. PMID: 31541153; PMCID: PMC6754408.
16. Liu K, Chen Y, Lin R, et al. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect. 2020 Jun;80(6):e14–8. 10.1016/j.jinf.2020.03.005. Epub 2020 Mar 27. PMID: 32171866; PMCID: PMC7102640.
17. Shao J, Fan R, Guo C 4 et al. Composite interventions on outcomes of severely and critically ill patients with COVID-19 in Shanghai, China.medRxiv preprint doi: https://doi.org/10.1101/2023.05.10.23289325; this version posted May 16, 2023.
18. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020 Jun;80(6):607–13. 10.1016/j.jinf.2020.03.037. Epub 2020 Apr 10. PMID: 32283152; PMCID: PMC7194613.
19. Chang YC, Chen YC, Huang CC et al. Clinical effectiveness of molnupiravir in patients with COVID-19 undergoing haemodialysis. Int J Antimicrob Agents. 2023 Apr 30;62(1):106834. doi: 10.1016/j.ijantimicag.2023.106834. Epub ahead of print. PMID: 37127127; PMCID: PMC10148756.
20. Radcliffe C, Palacios CF, Azar MM, et al. Real-world experience with available, outpatient COVID-19 therapies in solid organ transplant recipients during the omicron surge. Am J Transplant. 2022 Oct;22(10):2458–63. 10.1111/ajt.17098. Epub 2022 May 30. PMID: 35583664; PMCID: PMC9348251.
21. Kale A, Shelke V, Dagar N et al. How to use COVID-19 antiviral drugs in patients with chronic kidney disease. Front Pharmacol 2023 Feb 9;14:1053814. doi: 10.3389/fphar.2023.1053814. PMID: 36843922; PMCID: PMC9947246.
22. Ganatra S, Dani SS, Ahmad J et al. Oral nirmatrelvir and ritonavir in non-hospitalized vaccinated patients with Covid-19. Clin Infect Dis 2022 August 20 (Epub ahead of print).

23. Dryden-Peterson S, Kim A, Kim AY et al. Nirmatrelvir plus ritonavir for early COVID-19 and hospitalization in a large US health system. medRxiv [Preprint]. 2022 Jun 17:2022.06.14.22276393. doi: 10.1101/2022.06.14.22276393. Update in: Ann Intern Med. 2022 Dec 13;: PMID: 35734084; PMCID: PMC9216724.

Tables

Table 1. The demographic and clinical characteristics of all participants before and after the propensity score matching

Characteristics	Before matching			After 1:1 propensity-score matching		
	Controls N=3497	Azvudine N=434	*P* for difference	Matched controls N=428	Azvudine N=428	*P* for difference
Age	67.2±19.7	63.0±23.0	<0.001	61.1±22.6	62.7±23.0	0.29
Sex	2075 (59.3%)	263 (60.6%)	0.65	267 (62.4%)	259 (60.5%)	0.623
Primary diagnosis of COVID-19	2786 (79.7%)	418 (96.3%)	<0.001	409 (95.6%)	412 (96.3%)	0.73
Nucleic acid positive	1267 (36.2%)	300 (69.1%)	<0.001	308 (72.0%)	294 (68.7%)	0.331
Time from symptoms onset to admission			<0.001			0.628
0-5days	1298 (37.1%)	235 (54.1%)		246 (57.5%)	232 (54.2%)	
>5days	2107 (60.3%)	197 (45.4%)		180 (42.1%)	194 (45.3%)	
unclear	92 (2.6%)	2 (0.5%)		2 (0.5%)	2 (0.5%)	
Time from symptoms onset to treatment			<0.001			0.164
0-5days	1298 (37.1%)	220 (50.7%)		246 (57.5%)	218 (50.9%)	
>5days	2107 (60.3%)	212 (48.8%)		180 (42.1%)	208 (48.6%)	
unclear	92 (2.6%)	2 (0.5%)		2 (0.5%)	2 (0.5%)	
Days from symptoms onset to treatment	7.0 [3.0-14.0]	5.0 [3.0-10.0]	<0.001	4.0 [2.0-10.0]	5.0 [3.0-10.0]	0.001
Previous comorbidities						
Malignant tumor	695 (19.9%)	51 (11.8%)	<0.001	50 (11.7%)	50 (11.7%)	1
Transplantion	57 (1.6%)	15 (3.5%)	0.013	13 (3.0%)	14 (3.3%)	1
Liver disease	545 (15.6%)	76 (17.5%)	0.333	72 (16.8%)	72 (16.8%)	1
Diabetes mellitus	969 (27.7%)	114 (26.3%)	0.564	92 (21.5%)	112 (26.2%)	0.127
Chronic kidney disease	600 (17.2%)	77 (17.7%)	0.813	72 (16.8%)	73 (17.1%)	1
Hypertension	1702 (48.7%)	190 (43.8%)	0.061	164 (38.3%)	186 (43.5%)	0.144
Coronary heart disease	966 (27.6%)	113 (26.0%)	0.521	95 (22.2%)	110 (25.7%)	0.262
Cerebrovascular disease	682 (19.5%)	52 (12.0%)	<0.001	50 (11.7%)	52 (12.1%)	0.916
Alzheimer's disease	147 (4.2%)	13 (3.0%)	0.283	14 (3.3%)	13 (3.0%)	1
Rheumatoid disease	126 (3.6%)	8 (1.8%)	0.078	6 (1.4%)	8 (1.9%)	0.788
CCI	2.0 [0.0-3.0]	1.0 [0.0-3.0]	<0.001	1.0 [0.0-2.0]	1.0 [0.0-3.0]	0.203
Tocilizumab treatment	34 (1.0%)	21 (4.8%)	<0.001	13 (3.0%)	15 (3.5%)	0.848
Corticosteroids treatment	869 (24.8%)	189 (43.5%)	<0.001	163 (38.1%)	183 (42.8%)	0.186
Respiratory support on admission			0.112			0.145
no	1417 (40.5%)	184 (42.4%)		209 (48.8%)	184 (43.0%)	
require oxygen support	1894 (54.2%)	218 (50.2%)		199 (46.5%)	215 (50.2%)	
higher than High-flow nasal cannula	186 (5.3%)	32 (7.4%)		20 (4.7%)	29 (6.8%)	
eGFR			0.008			0.858
≥30ml/min/1.73m2	3058 (87.4%)	391 (90.1%)		390 (91.1%)	387 (90.4%)	
<30ml/min/1.73m2	332 (9.5%)	41 (9.4%)		37 (8.6%)	39 (9.1%)	
Clinical improvement score for day1	3.7±0.7	3.7±0.7	0.986	3.6±0.7	3.7±0.7	0.088

Table 2. All-cause death and clinical improvement outcomes in the Azvudine group versus matched controls.

Outcomes	Cumulative incidence (%)	Person-days	Crude incidence rate per 1000 person-days (95% CI)	HR (95% CI) [a]
All-cause death [b]				
Matched controls	50 (11.68%)	11068	4.52 (3.58–5.70)	Reference
Azvudine	32 (7.47%)	11363	2.82 (2.11–3.76)	0.63 (0.40–1.00)
Clinical improvement [c]				
Matched controls	330 (77.10%)	6339	52.06 (47.67–56.86)	Reference
Azvudine	347 (81.07%)	6000	57.83 (53.08–63.01)	1.03 (0.88–1.21)

HR: hazard ratio; CI: confidence interval

[a] HR was estimated using Cox proportional hazard regrssion

[b] Defined as all-cause mortality within 28-days follow-up

[c] Defined as 2 points or higher improvement in clinical symptoms within 28-days follow-up

Figures

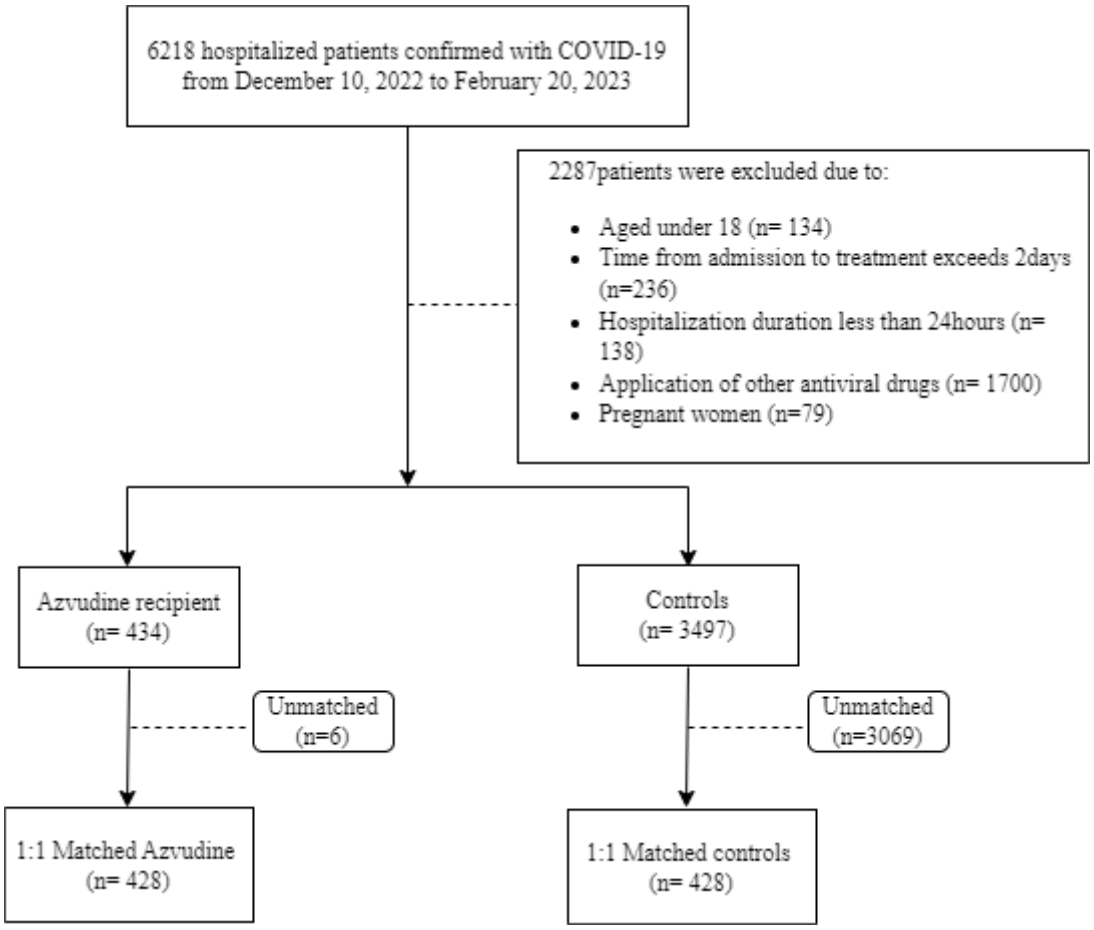

Figure 1

Identification of Azvudine recipient and control group in this study

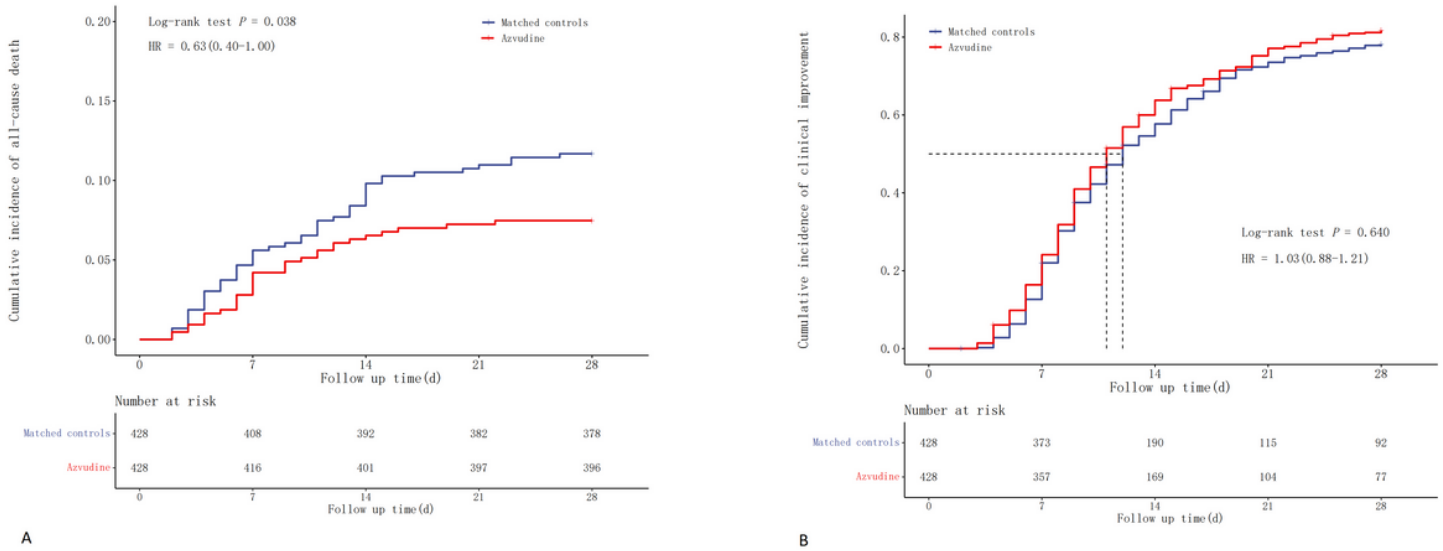

Figure 2

The cumulative incidence of all-cause death (A) and clinical improvement (B) in the Azvudine group versus matched controls.

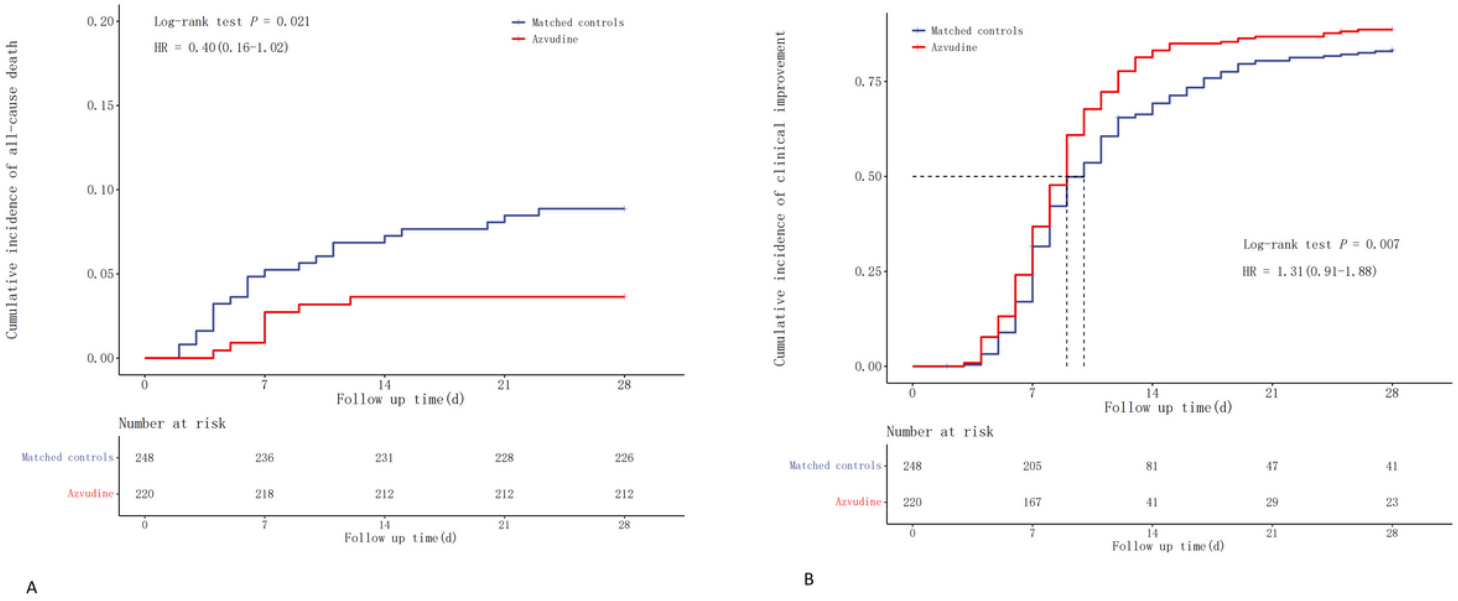

Figure 3

The cumulative incidence of all-cause death (A) and clinical improvement (B) in the Azvudine group (received Azvudine within 5 days from the onset of symptoms) versus matched controls.

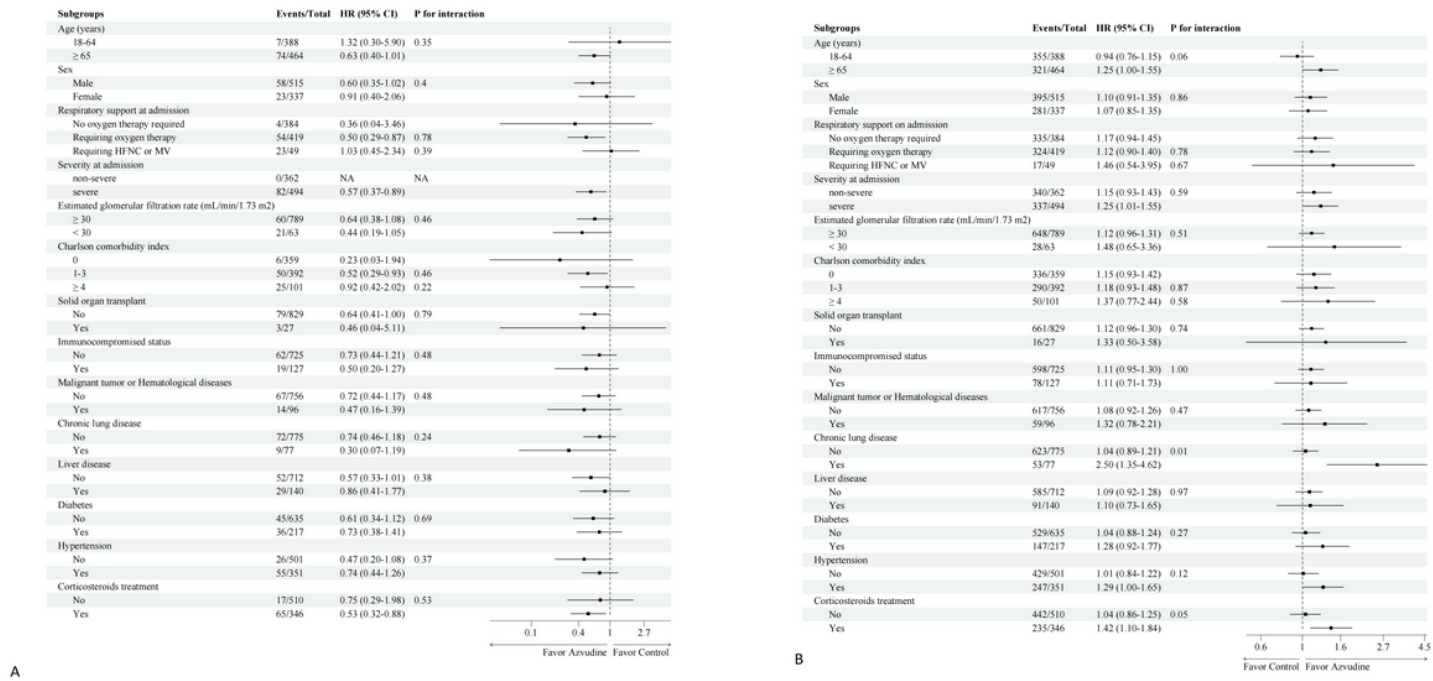

Figure 4

The subgroup analysis of the effectiveness of Azvudine treatment in reducing all-cause death (A) and improving clinical improvement (B)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigureS1..png
- FigureS2.A.png
- FigureS2.B.png