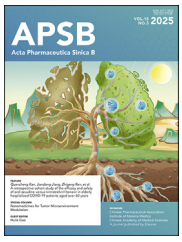
Acta Pharmaceutica Sinica B 2025;15(3):1333−1343

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



CLINICAL TRIALS

A retrospective cohort study of the efficacy and safety of oral azvudine *versus* nirmatrelvir/ritonavir in elderly hospitalized COVID-19 patients aged over 60 years

Bo Yu[a,†], Haiyu Wang[b,†], Guangming Li[c,†], Junyi Sun[b,†], Hong Luo[d,†], Mengzhao Yang[b], Yanyang Zhang[e], Ruihan Liu[f], Ming Cheng[g], Shixi Zhang[h], Guotao Li[i], Ling Wang[j], Guowu Qian[k], Donghua Zhang[l], Silin Li[m], Quancheng Kan[n,*], Jiandong Jiang[o,*], Zhigang Ren[b,*]

[a]*Department of Pharmacy, the First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China*
[b]*Department of Infectious Diseases, State Key Laboratory of Antiviral Drugs, Pingyuan Laboratory, the First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China*
[c]*Department of Liver Disease, the Affiliated Infectious Disease Hospital of Zhengzhou University, Zhengzhou 450052, China*
[d]*Guangshan County People's Hospital, Guangshan County, Xinyang 465450, China*
[e]*Henan Center for Disease Control and Prevention, Zhengzhou 450016, China*
[f]*Xiangya Medical College, Central South University, Changsha 410028, China*
[g]*Department of Medical Information, the First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China*
[h]*Department of Infectious Diseases, Shangqiu Municipal Hospital, Shangqiu 476000, China*
[i]*Department of Infectious Diseases, Luoyang Central Hospital Affiliated of Zhengzhou University, Luoyang 471000, China*
[j]*Department of Clinical Laboratory, Henan Provincial Chest Hospital Affiliated of Zhengzhou University, Zhengzhou 450008, China*
[k]*Department of Gastrointestinal Surgery, Nanyang Central Hospital, Nanyang 473009, China*
[l]*Department of Infectious Diseases, Anyang City Fifth People's Hospital, Anyang 455000, China*
[m]*Department of Respiratory and Critical Care Medicine, Fengqiu County People's Hospital, Xinxiang 453300, China*
[n]*Henan Key Laboratory of Precision Clinical Pharmacy, Zhengzhou University, Zhengzhou 450052, China*
[o]*State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100050, China*

Received 29 June 2024; received in revised form 15 November 2024; accepted 12 December 2024

*Corresponding authors.
E-mail addresses: kanqc@zzu.edu.cn (Quancheng Kan), jiang.jdong@163.com (Jiandong Jiang), fccrenzg@zzu.edu.cn (Zhigang Ren).
[†]These authors made equal contributions to this work.
Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2024.12.032

KEY WORDS

COVID-19;
Azvudine;
Paxlovid;
Elderly;
Comparative study;
Real-world;
Effectiveness;
Safety

Abstract Azvudine and nirmatrelvir/ritonavir (Paxlovid) are recommended for COVID-19 treatment in China, but their safety and efficacy in the elderly population are not fully known. In this multicenter, retrospective, cohort study, we identified 5131 elderly hospitalized COVID-19 patients from 32,864 COVID-19 patients admitted to nine hospitals in Henan Province, China, from December 5, 2022, to January 31, 2023. The primary outcome was all-cause death, and the secondary outcome was composite disease progression. Propensity score matching (PSM) was performed to control for confounding factors, including demographics, vaccination status, comorbidities, and laboratory tests. After 2:1 PSM, 1786 elderly patients receiving azvudine and 893 elderly patients receiving Paxlovid were included. Kaplan−Meier and Cox regression analyses revealed that compared with Paxlovid group, azvudine could significantly reduce the risk of all-cause death (log-rank $P = 0.002$; HR: 0.71, 95% CI: 0.573−0.883, $P = 0.002$), but there was no difference in composite disease progression (log-rank $P = 0.52$; HR: 1.05, 95% CI: 0.877−1.260, $P = 0.588$). Four sensitivity analyses verified the robustness of above results. Subgroup analysis suggested that a greater benefit of azvudine over Paxlovid was observed in elderly patients with primary malignant tumors (P for interaction $= 0.005$, HR: 0.32, 95% CI: 0.18−0.57) compared to patients without primary malignant tumors. Safety analysis revealed that azvudine treatment had a lower incidence of adverse events and higher lymphocyte levels than Paxlovid treatment. In conclusion, azvudine treatment is not inferior to Paxlovid treatment in terms of all-cause death, composite disease progression and adverse events in elderly hospitalized COVID-19 patients.

1. Introduction

As of April 2024, the cumulative number of coronavirus disease 2019 (COVID-19) worldwide reached 705 million, and the cumulative number of deaths reached 7.01 million. The vast majority of infected patients are mild or common, and only a small number are severe or critical[1]. Elderly individuals account for a large proportion of severely ill and hospitalized patients and have a high mortality rate[2,3]. This may be because older patients often have chronic diseases, which can cause difficulties in subsequent treatment[4]. Therefore, it is particularly important to explore treatment options for COVID-19 patients aged over 60 years.

Several drugs have been developed for the treatment of COVID-19, including nirmatrelvir/ritonavir (Paxlovid), molnupiravir and azvudine[5,6]. Among them, Paxlovid, a 3CL protease inhibitor, has been shown to be effective in reducing the risk of severe COVID-19 or death, especially in elderly patients, immunosuppressed patients, and patients with underlying neurological or cardiovascular disease[7,8]. Accordingly, in February 2022, Paxlovid received conditional emergency approval in China for the treatment of adult patients with mild-to-moderate COVID-19 with risk factors for progression to severe disease[9]. However, a study has also shown that Paxlovid is not significantly effective in reducing elderly severe patients with COVID-19[10]. Thus, the effect of Paxlovid needs to be further demonstrated.

Azvudine, the first oral small-molecule COVID-19 therapeutic drug developed in China, received conditional approval in July 2022 for the treatment of adult patients with COVID-19[11]. Azvudine belongs to the class of nucleoside reverse transcriptase inhibitors, which was originally developed to treat HIV-1 infection. Azvudine inhibits viral replication by blocking the transcription of viral RNA into DNA through inhibiting the reverse transcriptase activity of the virus. In the case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), although the primary mechanism of replication is different from that of HIV-1, azvudine remains effective in interfering with the virus's RNA-dependent RNA polymerase, a key enzyme in the viral replication process. In this way, azvudine slows or stops the replication and spread of SARS-CoV-2[12,13]. Moreover, azvudine is selectively triphosphorylated in the thymus and has also been shown to reduce the viral load, restore thymus function, improve lymphocyte profiles, and reduce inflammation and organ damage[14,15]. Our previous randomized, open-label, controlled clinical trial revealed that azvudine reduces the time to negative nucleic acid conversion[16]. Azvudine treatment significantly reduced early mortality in patients with moderate to severe COVID-19, among whom 42.77% were aged 80 years or older[17]. These two drugs are the main drugs currently used against COVID-19 in China, but most health care organizations tend to choose Paxlovid over azvudine worldwide. Thus, azvudine needs more international recognition, especially for elderly patients aged over 60 years.

Therefore, we conducted this large-scale, multicenter, retrospective, cohort study to investigate the efficacy and safety of oral azvudine compared with Paxlovid in hospitalized patients with SARS-CoV-2 infection.

2. Methods

2.1. Study design and population

This multicenter, retrospective, cohort study was conducted in Henan Province, China, in which hospitalized patients who tested positive for SARS-CoV-2 at nine hospitals from December 5, 2022, to January 31, 2023, including the First Affiliated Hospital of Zhengzhou University, Henan Provincial Chest Hospital, Henan Infectious Diseases Hospital, Luoyang Central Hospital, Nanyang Central Hospital, the Fifth People's Hospital of Anyang, Shangqiu Municipal Hospital, Guangshan County People's Hospital, and Fengqiu County People's Hospital were enrolled.

The study specifically targeted COVID-19 patients aged over 60 years who received standard treatment along with either azvudine or Paxlovid. Patients who did not receive antiviral agents, who received other antiviral regimens, or who had contraindications to azvudine or Paxlovid (such as severe liver and kidney impairments or the use of drugs highly dependent on CYP3A for clearance) were excluded from the study. All patients included in the study received standard diagnosis and treatment in accordance with the "COVID-19 diagnosis and treatment guidelines (trial version 9 or version 10)" issued by the National Health Commission of the People's Republic of China[5,18].

2.2. Data sources

Information on demographic characteristics, dates of hospital admissions, ICU admissions, registered deaths, diagnoses, prescriptions, drug dispensing records, imaging data, and laboratory tests was gathered from the electronic medical records of patients at nine hospitals.

2.3. Procedures

Prior to study commencement, participants meeting the criteria were assigned to either the azvudine group (receiving 5 mg once daily for a maximum of 14 days) or the Paxlovid group (receiving nirmatrelvir 300 mg and ritonavir 100 mg twice daily for a duration of 5 days) on the basis of their medication history and dispensing records. The reference date for this investigation was established as the day of confirmed SARS-CoV-2 infection. The clinical characteristics and confounding factors between the Paxlovid and azvudine groups were well balanced through propensity score matching (PSM) at a ratio of 1:2, including age, gender, BMI, severity of SARS-CoV-2 infection at admission, vaccination doses, concomitant systemic steroid or antibiotics at admission, comorbidities, and laboratory results. Patients were followed from the reference date to the occurrence of the outcome events or up to 31 days.

This study was endorsed by the research ethics committee at the First Affiliated Hospital of Zhengzhou University and authorized under approval number 2023-KY-0865-001. This study has also completed registration on ClinicalTrials.gov with the number NCT06349655. The study protocol complied with the STROBE guidelines and the ethical principles set out in the 1975 Declaration of Helsinki.

2.4. Outcomes

The primary outcome of this study was all-cause death, and the secondary outcome was composite disease progression. All-cause death was ascertained *via* electronic medical records. Composite disease progression was defined as progression to severe disease in patients with mild or moderate COVID-19, or death in all patients.

The safety outcomes were overall adverse events (AEs) and grade $\geq$3 AEs. AEs were defined in accordance with the Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE 5.0)[19]. The main adverse events identified in this study were abnormal laboratory results. The collection starting point was defined as after drug use, and the follow-up endpoint was defined as 5 half-lives after the last dose. When the severity of an adverse event changed, the most severe grade was used.

2.5. Definition of covariates

Demographic information, including age, sex, body mass index (BMI), and vaccination doses was collected. Upon admission, patients were categorized as having "mild", "moderate", or "severe" conditions on the basis of the "COVID-19 diagnosis and treatment guidelines (trial version 9 or version 10)". The use of systemic steroid therapy or antibiotics within 24 h of admission was classified as either "No" or "Yes". The timing of azvudine and Paxlovid administration was categorized as ">5 days" or "0−5 days" from the initial diagnosis.

Mild cases were defined by the presence of only representative respiratory tract infection symptoms. Moderate cases were characterized by a continuous high fever lasting more than 3 days, a respiratory rate below 30 breaths per minute, or oxygen saturation above 93%, along with characteristic COVID-19 findings on imaging. Severe disease was defined as a respiratory rate $\geq$30 breaths/minute, a resting oxygen saturation $\leq$93%, a $PaO_2/FiO_2 \leq$ 300 mmHg, lung lesions progressing >50% at 24−48 h, the need for mechanical ventilation, shock, or intensive care unit (ICU) monitoring.

At the time of diagnosis, laboratory results included neutrophil (Neut), lymphocyte (Lymph), glucose (Glu), high-density lipoprotein (HDL), low-density lipoprotein (LDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (CREA), the glomerular filtration rate (GFR), C-reactive protein (CRP), procalcitonin (PCT), prothrombin time (PT), activated partial thromboplastin time (APTT), cholesterol (CH), triglyceride (TG), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), albumin (ALB), and total bilirubin (TBIL) levels. Information regarding the presence of diabetes, hypertension, liver diseases, cardio-cerebral diseases, kidney diseases, primary malignant tumors, chronic respiratory diseases, and autoimmune diseases was extracted from electronic records.

2.6. Statistical analysis

In this research, data analysis was conducted *via* R v. 4.0.3. Statistical significance was determined as a two-tailed *P* value of less than 0.05. For normally distributed continuous variables, the mean and standard deviation were reported, whereas the median and interquartile range were used for nonnormally distributed variables. Group differences in continuous variables were assessed *via* independent *t* tests or Mann−Whitney U tests, as appropriate. Categorical variables are expressed as the frequencies and percentages, and group differences were analyzed with the chi-square test. We did multiple imputation *via* the "mice" package in R to fill in the missing data. Specifically, the first step is to generate a random distribution of missing variables through a regression model, and then randomly select the imputed values used to replace the missing values, and set the number of imputations to 5 times to generate 5 different filled datasets. In the second step, the required statistical analysis is performed on each complete data set to obtain the corresponding parameter estimates and standard errors. In the third step, according to the Rubin's rules, the analysis results of each dataset are adjusted for weighted average and variance to obtain the final parameter estimate and standard error.

To limit the impact of confounding variables on intervention assessment, a greedy match in a 1:2 ratio was employed to match baseline characteristics (including age, sex, severity, BMI, concomitant antibiotics use, vaccination doses, concomitant

systemic steroid use, time from diagnosis to treatment initiation, laboratory results and comorbidities) between the Paxlovid and azvudine groups *via* logistic regression. The clinical characteristics of the two groups were well balanced if the standardized mean differences were <0.1 and $P > 0.05$.

The Kaplan−Meier method was used to create cumulative event curves, and the log-rank test was used to determine the survival difference between groups. Cox proportional hazard regression models were constructed to evaluate hazard ratios (HRs) with 95% confidence intervals (CIs) for both primary and secondary outcomes while adjusting for all baseline covariates. The assumption of proportional hazards was assessed *via* Schoenfeld residuals, and multicollinearity was tested with the variance inflation factor (VIF), with a VIF value greater than 5 indicating multicollinearity. Subgroup analysis stratified by various factors, such as sex, age, severity, and comorbidities, was conducted. To assess the robustness of the study findings, four sensitivity analyses were performed. First, missing values were imputed using the mean, and a logistic regression model was used to perform a 1:2 greedy match to compare the reliability of the results. Second, a Probit model was adopted for a 1:2 greedy match. Third, taking into consideration the time needed for the drug to take effect after administration, individuals who were discharged from the hospital on the first day after admission were excluded, thereby narrowing the study population. Fourthly, we performed inverse probability of treatment weighting (IPTW) with propensity scores by creating a pseudo-population to get the most out of our data.

3. Results

3.1. Baseline characteristics

We identified 5131 elderly patients with COVID-19 from nine hospitals in Henan Province from December 5, 2022, to January 31, 2023, after strict inclusion and exclusion (Fig. 1). We subsequently performed 2:1 PSM to control for underlying confounders and ultimately included 1786 elderly COVID-19 patients receiving azvudine treatment and 893 elderly COVID-19 patients receiving Paxlovid treatment.

Before matching, the mean age was 75.28 years in the azvudine group and 76.04 years in the Paxlovid group ($P < 0.017$, standardized mean difference (SMD) < 0.1) (Table 1). There were many imbalances in variables between the two groups, such as sex, severity at admission, time from diagnosis to treatment exposure, concomitant antibiotics, concomitant systemic steroids, liver diseases, cardio-cerebral diseases, kidney diseases, primary malignant tumors, chronic respiratory diseases, autoimmune diseases neutrophils, low-density lipoprotein, prothrombin time, activated partial thromboplastin time, alkaline phosphatase, albumin, and total bilirubin. After matching, all variables were well controlled between the two groups, and there were no significant differences (Supporting Information Fig. S1). The mean age of the patients was 75.91 years in the azvudine group and 76.04 years in the Paxlovid group.

3.2. Primary outcomes

The primary outcome was all-cause death. During follow-up, there were 206 events in the azvudine group and 146 events in the Paxlovid group. The Kaplan−Meier method revealed that the azvudine group had a lesser risk of all-cause death than the Paxlovid group did ($P = 0.002$) (Fig. 2A).

The crude incidence rate of all-cause death was 9.22 per 1000 person-days in the azvudine group and 12.89 per 1000 person-days in the Paxlovid group (Fig. 3). Furthermore, all baseline variables were further controlled by the Cox multivariate regression model, and the results revealed that the risk of all-cause death was 29% lesser in the azvudine group than in the Paxlovid group (HR: 0.71, 95% CI: 0.573−0.883, $P = 0.002$) (Fig. 3).

We further stratified patients according to sex, severity, vaccination doses, concomitant antibiotics use, concomitant systemic steroid use, time from diagnosis to treatment exposure, diabetes, hypertension, liver disease, cardio-cerebral diseases, kidney disease, primary malignant tumors, chronic respiratory diseases, and autoimmune diseases for subgroup analysis (Table 2). For all-cause death, potentially meaningful interactions suggesting a greater benefit of azvudine over Paxlovid were observed in elderly patients with primary malignant tumors compared to patients without primary malignant tumors (P for interaction = 0.005, HR: 0.32, 95% CI: 0.18−0.57).

3.3. Secondary outcomes

The secondary outcome was composite disease progression. During follow-up, 346 events occurred in the azvudine group, and 189 events occurred in the Paxlovid group. The risk of the composite disease progression outcome was not significantly different between the two groups according to the Kaplan−Meier method ($P = 0.52$) (Fig. 2B). The crude incidence rate of composite disease progression was 17.52 per 1000 person-days in the azvudine group and 18.16 per 1000 person-days in the Paxlovid group. A Cox multivariate regression model revealed that there was no significant difference in the risk of composite disease progression between the azvudine and Paxlovid groups (HR: 1.05, 95% CI: 0.877−1.260, $P = 0.588$) (Fig. 3). Subgroup analyses suggested that for composite disease progression, potentially meaningful interactions suggesting a greater benefit of azvudine over Paxlovid were observed in elderly patients with one dose of vaccination compared to patients with other doses of vaccination (P for interaction = 0.048, HR: 0.54, 95% CI: 0.29−0.99) (Table 2).

3.4. Sensitivity analysis

Four sensitivity analyses were conducted to test the robustness of our results. First, we used the mean for the imputation of missing data. The baseline characteristics are shown in Supporting Information Table S1. Compared with the Paxlovid group, the azvudine group had a lesser risk of all-cause death according to the Kaplan−Meier curve ($P = 0.0072$, Supporting Information Fig. S2A) and Cox regression analysis (HR: 0.78, 95% CI: 0.628−0.964, $P = 0.022$; Supporting Information Fig. S3). The risk of composite disease progression between the two groups was not significantly different according to the Kaplan−Meier curve ($P = 0.74$, Fig. S2B) or Cox regression analysis (HR: 1.13, 95% CI: 0.944−1.353, $P = 0.184$; Fig. S3).

Second, we used a Probit regression model for PSM, and the baseline characteristics were well balanced between the two groups ($P > 0.05$, Supporting Information Table S2). The risk of all-cause death was significantly lesser in the azvudine group than in the Paxlovid group according to the Kaplan−Meier curve ($P = 0.00053$, Supporting Information Fig. S4A) and Cox

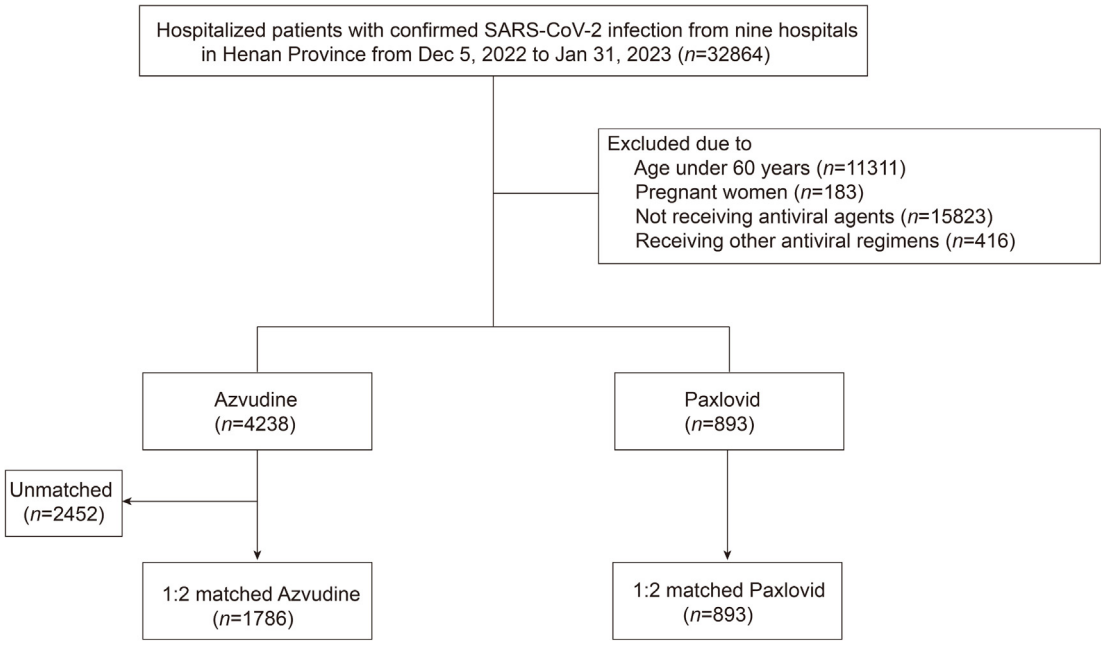


Figure 1 Flowchart of the study design.

regression (HR: 0.74, 95% CI: 0.597−0.924, $P = 0.008$; Supporting Information Fig. S5). There was no significant difference in composite disease progression between the two groups ($P = 0.50$, Fig. S4B; HR: 1.09, 95% CI: 0.911−1.314, $P = 0.335$; Fig. S5).

Third, we excluded patients who were discharged from the hospital or died after the same day of medication (Supporting Information Table S3). Compared with the Paxlovid group, the azvudine group was associated with a lesser risk of all-cause death ($P = 0.00086$, Fig. S6A; HR: 0.69, 95% CI: 0.556−0.863, $P = 0.001$, Supporting Information Fig. S7) but did not have an increased risk of composite disease progression ($P = 0.35$, Fig. S6B; HR: 1.00, 95% CI: 0.833−1.202, $P = 0.994$, Fig. S7).

Finally, we performed IPTW to expand the sample size. The baseline characteristic of two groups were shown in Supporting Information Table S4. Kaplan−Meier analysis (Supporting Information Fig. S8) shows that azvudine continues to have significant efficacy in reducing all-cause mortality ($P = 0.001$) and composite disease progression ($P = 0.0005$). Cox regression analysis (Supporting Information Fig. S9) revealed that azvudine could reduce 31% risk of all-cause death (95% CI: 0.549−0.858, $P = 0.001$), but had no significant difference in the risk of composite disease progression (HR: 1.00, 95% CI: 0.828−1.208, $P = 0.998$) *versus* Paxlovid.

3.5. *Safety analysis*

We assessed and compared the safety of azvudine and Paxlovid in elderly patients with COVID-19 by assessing adverse events in both groups (Table 3). Compared with the Paxlovid group, the azvudine group presented decreases of all grades AEs, including lymphocyte count decreased ($P = 0.028$), PLT count decreased ($P = 0.001$), ALT increased ($P < 0.001$), AST increased ($P = 0.006$), hypercholesterolemia ($P = 0.008$). For Grade ≥3 AEs, the Paxlovid group was associated with a greater risk of lymphocyte count decreased ($P = 0.003$) compared with azvudine group.

3.6. *Dynamic changes in leukocyte subsets*

We further investigated the dynamic changes in leukocyte subsets in both the azvudine and Paxlovid groups within 15 days of drug administration. The results revealed that neutrophil counts were above the normal range in both groups, and with significant differences between the two groups after treatment at some time points (Fig. 4A). The lymphocyte counts of the patients in the two groups were below normal, while the lymphatic counts of the patients in the azvudine group were higher than those in Paxlovid group (Fig. 4B). Eosinophil levels were significantly decreased in both groups, with significant differences between the two groups at some time points (Fig. 4C). Monocyte levels were within the normal range between the two groups, and there was essentially no significant difference (Fig. 4D).

4. Discussion

In this multicenter, large-data cohort study, we confirmed that azvudine is not inferior to Paxlovid in terms of efficacy and safety in elderly COVID-19 patients over 60 years of age and is even more effective in reducing the risk of all-cause mortality. The sample size of up to 32,864 patients further reduces the possible bias in our results. In subgroup analyses stratified by age, sex, different number of vaccine vaccinations, concomitant use of systemic steroids or antibiotics, having diabetes mellitus, hypertension, hepatic, renal, cardio-cerebral, chronic respiratory, and autoimmune conditions, consistent results were observed, and it is noteworthy that in patients with malignant tumors, the effect of azvudine was stronger than that of Paxlovid, especially in reducing the risk of all-cause mortality.

In previous retrospective studies that used only one method or subgroup analysis[10], four sensitivity analyses were used to verify the robustness of the results. First, to reduce the effect of missing value imputation, we reanalyzed the data *via* mean imputation instead of multiple imputation. Second, we used PSM with Probit

Table 1 Baseline characteristics of elderly patients with COVID-19 before and after propensity score matching.

Characteristics	Before matching			After 2:1 matching		
	Azvudine (n = 4238)	Paxlovid (n = 893)	P value	Azvudine (n = 1786)	Paxlovid (n = 893)	P value
Age, mean (SD), year	75.28 (8.55)	76.04 (8.77)	0.017	75.91 (8.51)	76.04 (8.77)	0.707
Gender, n (%)			0.001			0.427
Male	2609 (61.6)	602 (67.4)		1175 (65.8)	602 (67.4)	
Female	1629 (38.4)	291 (32.6)		611 (34.2)	291 (32.6)	
BMI, mean (SD), kg/m^2	24.17 (3.80)	24.20 (3.66)	0.864	24.25 (3.89)	24.20 (3.66)	0.744
Severity at admission, n (%)			<0.001			0.511
Mild	206 (4.9)	36 (4.0)		77 (4.3)	36 (4.0)	
Moderate	2897 (68.4)	533 (59.7)		1101 (61.6)	533 (59.7)	
Severe[a]	1135 (26.8)	324 (36.3)		608 (34.0)	324 (36.3)	
Vaccination doses, n (%)			0.2			0.94
0 dose	1269 (29.9)	247 (27.7)		491 (27.5)	247 (27.7)	
1 dose	288 (6.8)	62 (6.9)		111 (6.2)	62 (6.9)	
2 doses	548 (12.9)	144 (16.1)		281 (15.7)	144 (16.1)	
3 doses	2081 (49.1)	429 (48.0)		882 (49.4)	429 (48.0)	
4 doses	51 (1.2)	11 (1.2)		21 (1.2)	11 (1.2)	
5 doses	1 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Time from diagnosis to treatment exposure, n (%)			<0.001			0.076
>5 days	719 (17.0)	305 (34.2)		548 (30.7)	305 (34.2)	
0−5 days	3519 (83.0)	588 (65.8)		1238 (69.3)	588 (65.8)	
Concomitant antibiotics, n (%)			<0.001			0.248
No	1845 (43.5)	547 (61.3)		1051 (58.8)	547 (61.3)	
Yes	2393 (56.5)	346 (38.7)		735 (41.2)	346 (38.7)	
Concomitant systemic steroid, n (%)			<0.001			0.596
No	2320 (54.7)	587 (65.7)		1154 (64.6)	587 (65.7)	
Yes	1918 (45.3)	306 (34.3)		632 (35.4)	306 (34.3)	
Comorbidities, n (%)						
Diabetes	1151 (27.2)	259 (29.0)	0.28	517 (28.9)	259 (29.0)	1
Hypertension	2015 (47.5)	396 (44.3)	0.088	789 (44.2)	396 (44.3)	0.967
Liver diseases	358 (8.4)	169 (18.9)	<0.001	293 (16.4)	169 (18.9)	0.116
Cardio-cerebral diseases	1526 (36.0)	382 (42.8)	<0.001	776 (43.4)	382 (42.8)	0.772
Kidney diseases	1174 (27.7)	180 (20.2)	<0.001	347 (19.4)	180 (20.2)	0.693
Primary malignant tumor	369 (8.7)	97 (10.9)	0.048	194 (10.9)	97 (10.9)	1
Chronic respiratory diseases	895 (21.1)	158 (17.7)	0.024	303 (17.0)	158 (17.7)	0.677
Autoimmune diseases	107 (2.5)	35 (3.9)	0.028	61 (3.4)	35 (3.9)	0.581
Laboratory parameters, mean (SD)						
Neutrophil, × 10^9/L	5.96 (4.09)	6.72 (4.80)	<0.001	6.59 (4.55)	6.72 (4.80)	0.497
Lymphocyte, × 10^9/L	1.08 (1.83)	1.11 (3.35)	0.716	1.11 (2.49)	1.11 (3.35)	0.995
Glucose, mmol/L	8.19 (4.17)	8.32 (4.12)	0.391	8.19 (4.16)	8.32 (4.12)	0.433
High-density lipoprotein, mmol/L	1.21 (2.42)	1.13 (1.79)	0.327	1.16 (2.04)	1.13 (1.79)	0.738
Low-density lipoprotein, mmol/L	2.37 (2.58)	2.18 (1.59)	0.037	2.17 (1.41)	2.18 (1.59)	0.843
Alanine aminotransferase, IU/L	34.98 (67.40)	38.86 (66.66)	0.117	37.06 (70.24)	38.86 (66.66)	0.524
Aspartate aminotransferase, IU/L	41.64 (81.11)	40.50 (50.92)	0.685	40.25 (55.19)	40.50 (50.92)	0.912
Creatine, μmol/L	91.94 (116.16)	89.39 (99.37)	0.542	88.10 (93.27)	89.39 (99.37)	0.742
Glomerular filtration rate, mL/min	78.66 (26.14)	79.70 (23.75)	0.269	79.71 (25.86)	79.70 (23.75)	0.993
C-reactive protein, mg/L	56.92 (65.25)	60.64 (67.32)	0.124	60.23 (70.43)	60.64 (67.32)	0.885
Procalcitonin, ng/mL	1.06 (6.98)	1.13 (5.89)	0.771	1.44 (9.39)	1.13 (5.89)	0.365
Prothrombin time, s	18.23 (11.32)	15.85 (10.39)	<0.001	15.80 (8.63)	15.85 (10.39)	0.905
Activated partial thromboplastin time, s	25.09 (11.20)	27.21 (14.07)	<0.001	27.52 (11.66)	27.21 (14.07)	0.548
Cholesterol, mmol/L	4.00 (2.25)	3.89 (2.30)	0.192	3.89 (1.96)	3.89 (2.30)	0.997
Triglyceride, mmol/L	1.47 (2.64)	1.37 (2.23)	0.299	1.39 (2.03)	1.37 (2.23)	0.803
Alkaline phosphatase, IU/L	81.57 (52.11)	87.26 (99.63)	0.014	85.68 (64.75)	87.26 (99.63)	0.623
Gamma-glutamyl transpeptidase, IU/L	55.41 (80.59)	57.32 (71.44)	0.511	58.10 (80.50)	57.32 (71.44)	0.806
Albumin, g/L	36.82 (31.85)	33.01 (9.02)	<0.001	32.97 (13.79)	33.01 (9.02)	0.94
Total bilirubin, μmol/L	12.36 (10.90)	11.53 (8.41)	0.033	11.78 (9.18)	11.53 (8.41)	0.492

[a]Patients with severe disease in this study are defined as patients with severe and critical disease in the guidelines.

regression rather than logistic regression to control for confounders. Third, given that it takes time for a drug to take effect, we excluded some patients who were discharged for improvement, death, or disease progression on the same day they received azvudine or Paxlovid. Fourth, considering that the matching method may be subject to some bias, we also verify the results

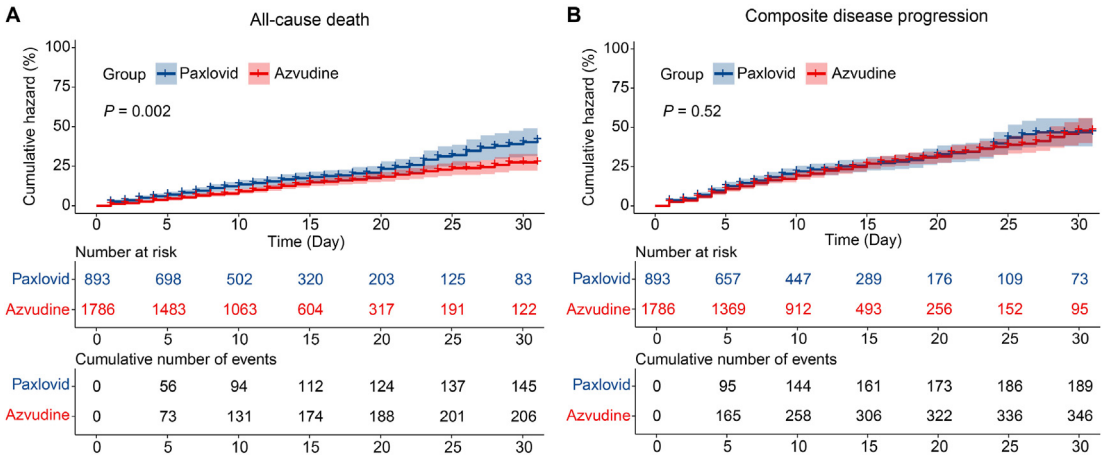


Figure 2 Kaplan−Meier curves of elderly patients with COVID-19 receiving azvudine treatment and those receiving Paxlovid treatment. Cumulative hazard of all-cause death (A) and composite disease progression (B).

with IPTW. All four sensitivity analysis methods described above confirmed the results of this paper, reaffirming the reliability of our results.

In addition, most previous studies controlled for only the effects of confounding factors, such as demographic characteristics, comorbidities, drug use and disease severity, and few studies controlled for the effects of laboratory test indices[20]. However, some studies have shown that increased age, a high neutrophil−lymphocyte ratio (NLR), and an elevated white blood cell count are associated with one-month mortality in COVID-19 patients[21]. AST, ALT, ALP, GGT, total bilirubin, and albumin, which are liver function indicators, are associated with disease severity and in-hospital mortality. In particular, the combination of the ALB level with the AST or total bilirubin level can significantly predict in-hospital mortality[22]. Several studies have pointed out that respiratory cells of COPD (chronic obstructive pulmonary disease) patients are more susceptible to SARS-CoV-2 infection, particularly due to the higher expression of the viral entry proteins ACE2 and TMPRSS2 on their cells. In addition, airway mucus cell hyperplasia in patients with chronic obstructive pulmonary disease provides more susceptible cells to the virus, thus increasing the risk of infection[23]. These results suggest that many laboratory test indicators may also be potential confounders; thus, we controlled for demographic characteristics, laboratory test indicators, and medication use, as well as the patient's own immunization profile, to further ensure the veracity and reliability of the statistical results.

Vaccination information and vaccination completion are important for disease development and clinical outcomes, so the vaccination status is a critical problem that cannot be ignored. To acquire information about vaccinations in the population included in this study, we specially connected our local responsible agency of Henan Provincial Center for Disease Control and Prevention to access the vaccination information during the study period. According to the available data, the vaccination coverage rate of hospitalized population enrolled in this study was 70.45%, and the unvaccinated hospitalized patients accounted for 29.55%. To eliminate the potential impact of vaccination status on drug-related clinical outcomes, we included the vaccination status in the propensity score matching (PSM). The results showed that compared with Paxlovid group, azvudine could significantly reduce the risk of all-cause death, but there was no difference in composite disease progression.

Thymic degeneration is an important cause of high mortality in elderly patients with COVID-19. Thymic atrophy or degeneration may lead to insufficient antiviral immunity and an excessive self-injury immune response in elderly individuals[24], and some studies have reported that thymic senescence potentially plays a role in

Variable	Events	PDs	Incidence	HR (95% CI)	*P* value
ALL−cause death					
Paxlovid	146	11324	12.89	1.00 (reference)	
Azvudine	206	22340	9.22	0.71 (0.573−0.883)	0.002
Composite disease progression					
Paxlovid	189	10405	18.16	1.00 (reference)	
Azvudine	346	19751	17.52	1.05 (0.877−1.260)	0.588

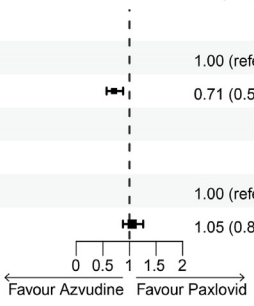


Figure 3 Multivariate Cox proportional hazards regression analysis of all-cause death and composite disease progression in elderly patients with COVID-19 receiving azvudine and Paxlovid. All the baseline covariates are adjusted for in Table 1. (A) Hazard ratio of all-cause death. (B) Hazard ratio of composite disease progression. HR, hazard ratio; 95% CI, 95% confidence interval. PDs, Person-days. Incidence: events/per 1000 PDs.

Table 2 Subgroup analyses for the different drug treatment effect on all-cause death and composite disease progression in the elderly COVID-19 patients according to baseline characteristics.

Characteristic	All-cause death		Composite disease progression	
	HR (95% CI)[a]	*P* value for interaction	HR (95% CI)[a]	*P* value for interaction
Gender				
Male	0.70 (0.55−0.90)	0.794	0.91 (0.74−1.12)	0.462
Female	0.77 (0.50−1.18)		1.06 (0.74−1.52)	
Severity at admission				
Mild	0.76 (0.18−3.20)	0.966	0.47 (0.09−2.33)	0.282
Moderate	0.75 (0.49−1.14)		0.80 (0.53−1.21)	
Severity	0.71 (0.55−0.92)		1.08 (0.88−1.31)	
Vaccination doses				
None	0.81 (0.57−1.17)	0.6	1.16 (0.85−1.59)	0.048
One dose	0.53 (0.27−1.04)		0.54 (0.29−0.99)	
Two doses	0.59 (0.34−1.03)		0.94 (0.59−1.50)	
Three doses	0.74 (0.53−1.03)		0.87 (0.67−1.14)	
Four doses	(0−lnf)		(0−lnf)	
Concomitant antibiotics, *n* (%)				
No	0.69 (0.51−0.92)	0.64	1.03 (0.80−1.32)	0.322
Yes	0.74 (0.54−1.00)		0.85 (0.66−1.09)	
Concomitant systemic steroid, *n* (%)				
No	0.63 (0.49−0.82)	0.107	0.92 (0.74−1.15)	0.677
Yes	0.90 (0.62−1.31)		0.97 (0.72−1.29)	
Time from diagnosis to treatment exposure				
>5 days	0.56 (0.39−0.82)	0.147	0.97 (0.72−1.31)	0.845
≤5 days	0.79 (0.61−1.03)		0.93 (0.74−1.15)	
Diabetes, *n* (%)				
No	0.69 (0.53−0.89)	0.568	0.93 (0.75−1.14)	0.805
Yes	0.79 (0.53−1.16)		0.99 (0.71−1.38)	
Hypertension, *n* (%)				
No	0.67 0.51−0.88)	0.446	0.85 (0.67−1.07)	0.186
Yes	0.79 (0.57−1.11)		1.1 (0.83−1.45)	
Liver diseases, *n* (%)				
No	0.68 (0.53−0.88)	0.338	0.95 (0.78−1.17)	0.995
Yes	0.85 (0.56−1.28)		0.94 (0.65−1.35)	
Cardio-cerebral diseases, *n* (%)				
No	0.63 (0.46−0.86)	0.303	0.92 (0.72−1.17)	0.792
Yes	0.79 (0.59−1.06)		0.97 (0.75−1.26)	
Kidney diseases, *n* (%)				
No	0.74 (0.58−0.95)	0.672	1.00 (0.80−1.23)	0.367
Yes	0.66 (0.44−0.99)		0.83 (0.60−1.14)	
Primary malignant tumor, *n* (%)				
No	0.81 (0.64−1.02)	0.005	0.98 (0.82−1.19)	0.161
Yes	0.32 (0.18−0.57)		0.64 (0.36−1.12)	
Chronic respiratory diseases, *n* (%)				
No	0.75 (0.60−0.94)	0.234	0.99 (0.82−1.21)	0.214
Yes	0.52 (0.29−0.93)		0.72 (0.46−1.12)	
Autoimmune diseases, *n* (%)				
No	0.71 (0.57−0.88)	0.739	0.96 (0.80−1.15)	0.231
Yes	0.89 (0.27−2.93)		0.54 (0.21−1.38)	

Abbreviation: HR, Hazard Ratio; 95% CI, 95% confidence interval.

[a]Efficacy outcome for Azvudine *versus* Paxlovid in different subgroup. Reference group: Paxlovid.

the clinical severity of elderly COVID-19 patients because T cells play an important role in anti-SARS-CoV-2 immunity[25]. Research has shown that COVID-19 infection leads to reduced T cell numbers and functional exhaustion, which is extremely detrimental to elderly individuals[26]. However, azvudine can selectively protect the thymus. Oral azvudine is highly enriched and phosphorylated in the thymus and helps to restore thymic function, improve lymphocyte profiles and immune function, alleviate inflammation and organ damage, and has shown promising results in the treatment of COVID-19 patients, most likely because azvudine provides an immunoprotective effect by activating T cells in thymic tissue through an effective phosphorylation process[14,15]. This effect is particularly important in elderly individuals. Azvudine can compensate for the reduction in T cells in older adults due to thymic atrophy or degeneration, thereby significantly reducing the risk of developing a serious illness in those over 60 years of age.

In addition, COVID-19 is different from AIDS and hepatitis B and C, and the effective antiviral treatment period is only 3−5 days, after which there could be dysregulated immunity and/or an

Table 3 Incidence of adverse event of elderly COVID-19 patients receiving Azvudine and Paxlovid.

Adverse events (*n*, %)	Available data[a]		All grades			Grade ≥ 3[b]		
	Azvudine	Paxlovid	Azvudine	Paxlovid	*P* value	Azvudine	Paxlovid	*P* value
Lymphocyte count decreased	1596	712	554 (35%)	281 (39%)	0.028	332 (21%)	188 (26%)	0.003
Lymphocyte count increased	1596	712	26 (1.6%)	10 (1.4%)	0.7	1 (<0.1%)	1 (0.1%)	0.5
Neutrophil count increased	756	526	28 (3.7%)	23 (4.4%)	0.5	6 (0.8%)	7 (1.3%)	0.3
PLT count decreased	1098	590	116 (11%)	94 (16%)	0.001	48 (4.4%)	37 (6.3%)	0.089
Anemia	787	540	325 (41%)	219 (41%)	0.8	74 (9.4%)	49 (9.1%)	0.8
Hypophosphatemia	418	406	74 (18%)	91 (22%)	0.091	0 (0%)	0 (0%)	
Hypokalemia	1245	668	301 (24%)	137 (21%)	0.069	109 (8.8%)	51 (7.6%)	0.4
Hyperkalemia	1245	668	44 (3.5%)	21 (3.1%)	0.7	1 (<0.1%)	0 (0%)	>0.9
ALT increased	994	536	234 (24%)	176 (33%)	<0.001	18 (1.8%)	18 (3.4%)	0.057
AST increased	1048	547	197 (19%)	135 (25%)	0.006	21 (2.0%)	16 (2.9%)	0.2
ALP increased	964	549	78 (8.1%)	38 (6.9%)	0.4	0 (0%)	1 (0.2%)	0.4
GGT increased	695	504	114 (16%)	98 (19%)	0.2	5 (0.7%)	4 (0.8%)	>0.9
Hyperuricemia	817	504	56 (6.9%)	26 (5.2%)	0.2	0 (0%)	0 (0%)	
CREA increased	1052	550	100 (9.5%)	67 (12%)	0.1	26 (2.5%)	11 (2.0%)	0.6
Hypoglycemia	329	56	49 (15%)	9 (16%)	0.8	0 (0%)	0 (0%)	
Hypercholesterolemia	193	92	11 (5.7%)	14 (15%)	0.008	0 (0%)	0 (0%)	
Hypertriglyceridemia	111	81	24 (22%)	16 (20%)	0.8	0 (0%)	0 (0%)	

Abbreviations: PLT, platelets; Hb, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; UA, uric acid; CREA, creatinine; Glu, glucose; CH, Cholesterol; TG, Triglyceride.

[a]Number of people who completed the follow-up of data collection for this indicator.

[b]Severity grades were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

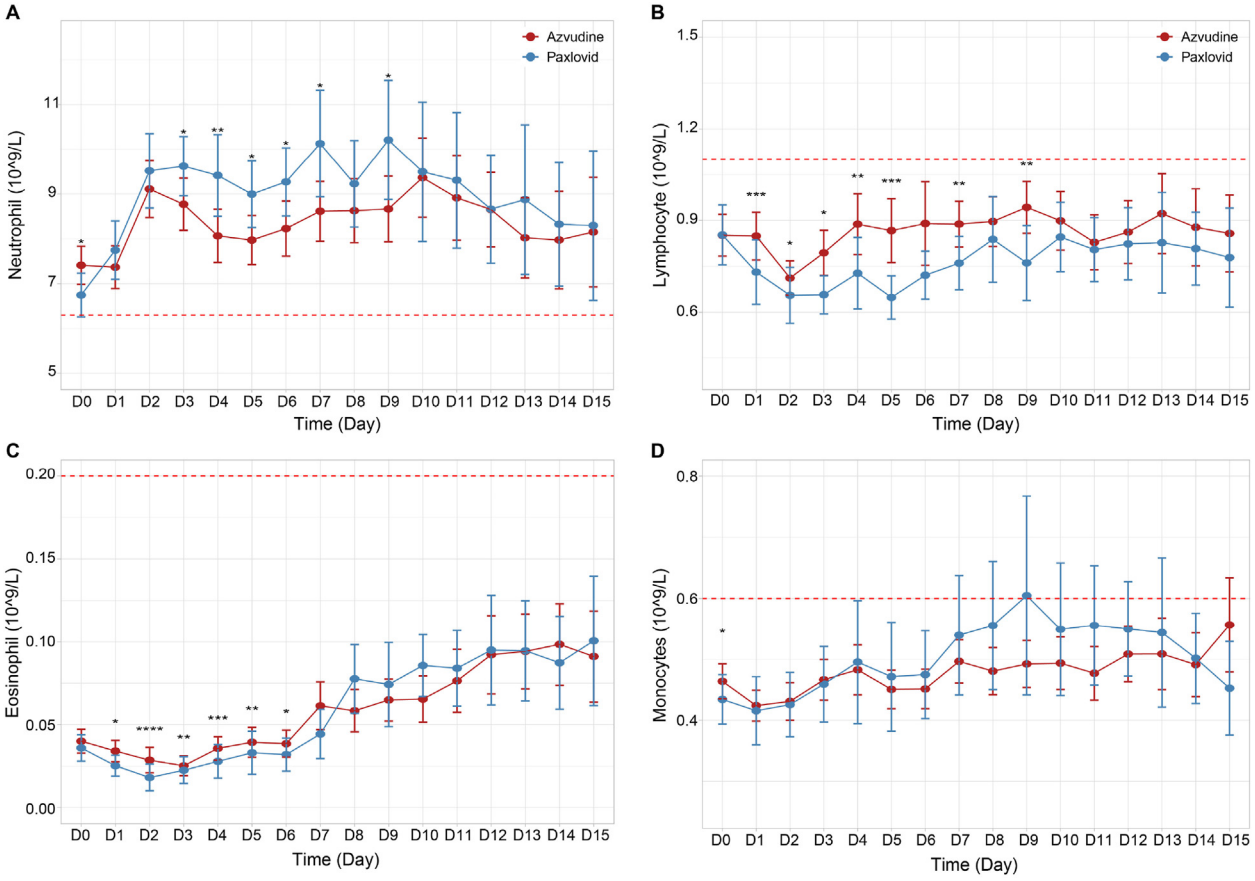


Figure 4 Dynamic changes in leukocyte subsets. After treatment, the dynamic levels of neutrophils (A), lymphocytes (B), eosinophils (C), and monocytes (D) in the azvudine and Paxlovid groups were measured.

inflammatory response; the effect of antiviral treatment could be greatly weakened at this stage[27]. As azvudine can protect the thymus gland from viral attack and improve the immune capacity of elderly individuals, the antiviral effect might continue after the first 3−5 days of SARS-CoV-2 infection. Paxlovid is an antiviral that has no effect on the body's immune system and does not alter inflammation or cytokine storms, which makes it less effective than azvudine in the middle−long-term range. Thus, one report found that Paxlovid had no significant effect on reducing the time to COVID-19 symptom remission and that the differences in hospitalization and mortality were not statistically significant[28]. Another study reported that Paxlovid had no significant therapeutic effect on vaccinated low-risk patients or those not at risk for serious disease[29]. Azvudine has the potential to treat both the symptoms and cause of the disease, with antiviral agents as the symptomatic manifestation and immune protection as the essence.

With respect to the side effects of this drug, studies have shown that although Paxlovid has no serious side effects, patients need to be monitored for kidney and liver function, as well as drug interactions[30]. Moreover, owing to the presence of the ritonavir component, Paxlovid has the potential to cause serious drug−drug interactions with other drugs metabolized *via* CYP3A4[31]. Patients over 60 years of age often have concomitant chronic diseases[32], which limits the dosing of Paxlovid to certain amounts. For example, coadministration of Paxlovid with statins for cholesterol may lead to significant drug interactions[33]. In contrast, no related side effects have been reported for azvudine compared with Paxlovid. Therefore, azvudine may be a safer treatment option (with respect to Paxlovid) for elderly patients over 60 years of age. In addition, Paxlovid is priced at approximately $1539.04 per treatment in the U.S.[34]. In China, even with government subsidies, Paxlovid costs as much as RMB 1890 per course of treatment due to failed negotiations to include it in the health insurance drug list. Azvudine, on the other hand, costs only RMB 270 per course of treatment, which is undoubtedly more advantageous for retired low-income seniors over 60 years old. Therefore, we recommend azvudine as the primary treatment for COVID-19 patients over 60 years of age.

There are several limitations in our study. Firstly, our results revealed that azvudine has a relatively favorable effect on patients with tumors, possibly because it can focus on the thymus, improve the lymphocyte profile, reduce inflammation and organ damage, and enhance the immunity of patients with tumors[15]. This may also be related to the fact that Paxlovid inhibits CYP3A4 metabolism and thus affects the action of antitumor drugs. However, this needs to be proven by further experimental studies. Secondly, although we included a large number of people, all were from Henan Province, without from other provinces or countries, which may limit the generalizability of our findings. In the future, we hope to have more regional data to supplement to support our results. Third, selection bias could be an unavoidable issue due to the retrospective nature of our research, such as the financial capacity, clinician treatment and patient preference. Finally, our study faced issues of immortal time bias due to the period between diagnosis and the exposure of medication.

5. Conclusions

In summary, we used five analytical methods to show that azvudine has a therapeutic effect similar to that of Paxlovid in elderly COVID-19 patients aged over 60 years. Notably, compared with patients without primary malignant tumors, patients with primary malignant tumors in the Paxlovid group presented a greater risk of all-cause death. Our results may provide valuable assistance in the selection of clinical treatment options.

Ethics approval and consent to participate

This study was reviewed and approved by the Institutional Review Board from The First Affiliated Hospital of Zhengzhou University (2023-KY-0865-001). Clinical trial registration number NCT06349655 on ClinicalTrials. Consent in written form was not required from all participants due to anonymity and retrospective study.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (82151525), National Key Research and Development Program of China (2022YFC2303100 and 2023YFC3043514), Young and Middle-aged Academic Leaders of Henan Provincial Health Commission (HNSWJW-2022013, China), the Scientific Research and Innovation Team of The First Affiliated Hospital of Zhengzhou University (QNCXTD2023002, China).

Author contributions

Bo Yu: Writing − review & editing, Writing − original draft, Formal analysis. Haiyu Wang: Writing − review & editing, Writing − original draft, Formal analysis, Data curation. Guangming Li: Writing − review & editing, Resources. Junyi Sun: Writing − review & editing, Formal analysis, Data curation. Hong Luo: Writing − review & editing, Resources. Mengzhao Yang: Writing − review & editing, Formal analysis, Data curation. Yanyang Zhang: Writing − review & editing, Resources. Ruihan Liu: Writing − review & editing, Resources. Ming Cheng: Writing − review & editing. Shixi Zhang: Writing − review & editing, Resources. Guotao Li: Writing − review & editing, Resources. Ling Wang: Writing − review & editing, Resources. Guowu Qian: Writing − review & editing, Resources. Donghua Zhang: Writing − review & editing, Resources. Silin Li: Writing − review & editing, Resources. Quancheng Kan: Writing − review & editing, Conceptualization. Jiandong Jiang: Writing − review & editing, Conceptualization. Zhigang Ren: Writing − review & editing, Funding acquisition, Conceptualization.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supporting information to this article can be found online at https://doi.org/10.1016/j.apsb.2024.12.032.

References

1. Worldometers. Coronavirus worldwide graphs. Published [2024-04-13]. Accessed [2024-04-13]. Available from: https://www.worldometers.info/coronavirus/worldwide-graphs/#google_vignette.

2. Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed Coronavirus Disease 2019—COVID-NET, 14 States, March 1−30, 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**:458−64.
3. CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States, February 12−March 16, 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**:343−6.
4. Hu C, Li J, Xing X, Gao J, Zhao S, Xing L. The effect of age on the clinical and immune characteristics of critically ill patients with COVID-19: a preliminary report. *PLoS One* 2021;**16**:e0248675.
5. The State Council the People's Republic of China. Notice on the issuance of the diagnosis and treatment protocol for coronavirus disease 2019 (Trial Tenth Edition). Published [2023-01-05]. Accessed [2024-04-15]. Available from: https://www.gov.cn/zhengce/zhengceku/2023-01/06/content_5735343.htm.
6. Zhao X, Cheng Y, Zhang M, Qianda B, Zhouma B, Yangzhen B, et al. Efficacy of nirmatrelvir-ritonavir *versus* azvudine for COVID-19 treatment in Tibet: a retrospective study. *Infect Drug Resist* 2023;**16**:6053−60.
7. Najjar-Debbiny R, Gronich N, Weber G, Khoury J, Amar M, Stein N, et al. Effectiveness of paxlovid in reducing severe coronavirus disease 2019 and mortality in high-risk patients. *Clin Infect Dis* 2023;**76**:e342−9.
8. Marzi M, Vakil M, Bahmanyar M, Zarenezhad E. Paxlovid: mechanism of action, synthesis, and *in silico* study. *BioMed Res Int* 2022; **2022**:7341493.
9. National Medical Products Administration. China grants conditional approval for Pfizer's oral COVID-19 drug. Published [2022-02-14]. Accessed [2024-04-13]. Available from: https://english.nmpa.gov.cn/2022-02/14/c_707085.htm.
10. Wang S, Sun J, Zhang X, Li M, Qin B, Liu M, et al. Antiviral effectiveness and survival correlation of azvudine and nirmatrelvir/ritonavir in elderly severe patients with COVID-19: a retrospective real-world study. *EClinicalMedicine* 2024;**69**:102468.
11. National Medical Products Administration. Domestically developed drug joins virus battle. Published [2022-08-15]. Accessed [2024-04-15]. Available from: http://english.nmpa.gov.cn/2022-08/15/c_797867.htm.
12. Wang R, Yang Q, Luo R, Peng Y, Dai S, Zhang X, et al. Azvudine, a novel nucleoside reverse transcriptase inhibitor showed good drug combination features and better inhibition on drug-resistant strains than lamivudine *in vitro*. *PLoS One* 2014;**9**:e105617.
13. Zhu K. Efficacy and safety evaluation of azvudine in the prospective treatment of COVID-19 based on four phase III clinical trials. *Front Pharmacol* 2023;**14**:1228548.
14. Zhang J, Li Y, Wang L, Liu H, Lu S, Liu Y, et al. Azvudine is a thymus-homing anti-SARS-CoV-2 drug effective in treating COVID-19 patients. *Signal Transduct Target Ther* 2021;**6**:414.
15. Sheng N, Li R, Li Y, Wang Z, Wang L, Li Y, et al. Selectively T cell phosphorylation activation of azvudine in the thymus tissue with immune protection effect. *Acta Pharm Sin B* 2024;**14**:3140−54.
16. Ren Z, Luo H, Yu Z, Song J, Liang L, Wang L, et al. A randomized, open-label, controlled clinical trial of azvudine tablets in the treatment of mild and common COVID-19, a pilot study. *Adv Sci* 2020;**7**:e2001435.
17. Chen R, Guo Y, Deng S, Wang J, Gao M, Han H, et al. All-cause mortality in moderate and severe COVID-19 patients with myocardial injury receiving *versus* not receiving azvudine: a propensity score-matched analysis. *Cardiol* 2023;**8**:103−10.
18. The State Council the People's Republic of China. Notice on the issuance of the diagnosis and treatment protocol for coronavirus disease 2019 (Trial Ninth Edition). [Accessed 15 April 2024]. Published [2022-03-14]. Accessed [2024-04-15]. Published [2022-03-14]. Accessed [2024-04-15]. Available from: https://www.gov.cn/zhengce/zhengceku/2022-03/15/content_5679257.htm.
19. U.S. Department Of Health And Human Services. Common terminology criteria for adverse events (CTCAE) version 5.0. Published [2017-11-27]. Accessed [2024-04-15]. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.
20. Sun Y, Jin L, Dian Y, Shen M, Zeng F, Chen X, et al. Oral azvudine for hospitalised patients with COVID-19 and pre-existing conditions: a retrospective cohort study. *EClinicalMedicine* 2023;**59**:101981.
21. Vafadar Moradi E, Teimouri A, Rezaee R, Morovatdar N, Foroughian M, Layegh P, et al. Increased age, neutrophil-to-lymphocyte ratio (NLR) and white blood cells count are associated with higher COVID-19 mortality. *Am J Emerg Med* 2021;**40**:11−4.
22. Tokarczyk U, Kaliszewski K, Kopszak A, Nowak Ł, Sutkowska-Stępień K, Sroczyński M, et al. Liver function tests in COVID-19: assessment of the actual prognostic value. *J Clin Med* 2022; **11**:4490.
23. Osan J, Talukdar S, Feldmann F, DeMontigny B, Jerome K, Bailey K, et al. Goblet cell hyperplasia increases SARS-CoV-2 Infection in chronic obstructive pulmonary disease. *Microbiol Spectr* 2022;**10**: e0045922.
24. Brunner S, Herndler-Brandstetter D, Weinberger B, Grubeck-Loebenstein B. Persistent viral infections and immune aging. *Ageing Res Rev* 2011;**10**:362−9.
25. Wang W, Thomas R, Oh J, Su D. Thymic aging may be associated with COVID-19 pathophysiology in the elderly. *Cells* 2021;**10**:628.
26. Liu R, Wang Y, Li J, Han H, Xia Z, Liu F, et al. Decreased T cell populations contribute to the increased severity of COVID-19. *Clin Chim Acta* 2020;**508**:110−4.
27. Beigel J, Tomashek K, Dodd L, Mehta A, Zingman B, Kalil A, et al. Remdesivir for the treatment of Covid-19—final report. *N Engl J Med* 2020;**383**:1813−26.
28. Hammond J, Fountaine R, Yunis C, Fleishaker D, Almas M, Bao W, et al. Nirmatrelvir for vaccinated or unvaccinated adult outpatients with Covid-19. *N Engl J Med* 2024;**390**:1186−95.
29. Gandhi R, Hirsch M. Treating acute Covid-19—final chapters still unwritten. *N Engl J Med* 2024;**390**:1234−6.
30. Mobinizadeh M, Akbarisari A, Olyaeemanesh A, Mohammadshahi M, Ahmadnezhad E, Aboee P, et al. Safety and efficacy of paxlovid in COVID-19 treatment: a rapid review. *Health Tech Asmnt Act* 2022;**6**. Available from: https://doi.org/10.18502/htaa.v6i1.11131.
31. Marzolini C, Kuritzkes D, Marra F, Boyle A, Gibbons S, Flexner C, et al. Recommendations for the management of drug−drug interactions between the COVID-19 antiviral nirmatrelvir/ritonavir (Paxlovid) and comedications. *Clin Pharmacol Ther* 2022;**112**:1191−200.
32. Tisminetzky M, Delude C, Hebert T, Carr C, Goldberg R, Gurwitz J. Age, multiple chronic conditions, and COVID-19: a literature review. *J Gerontol A Biol Sci Med Sci* 2022;**77**:872−8.
33. Vuorio A, Kovanen P, Raal F. Cholesterol-lowering drugs for high-risk hypercholesterolemia patients with COVID-19 while on Paxlovid™ therapy. *Future Virol* 2022;**17**:761−5.
34. Drugs-Price Guide. Paxlovid prices, coupons, copay cards & patient assistance. Published [2024-12-22]. Accessed [2024-12-26]. Available from: https://www.drugs.com/price-guide/paxlovid.