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CLINICAL TRIALS

# Real-world efficacy and safety of azvudine in hospitalized older patients with COVID-19 during the omicron wave in China: A retrospective cohort study

**Yuanchao Zhu[a,†], Fei Zhao[a,†], Yubing Zhu[b,†], Xingang Li[c,†], Deshi Dong[d,†], Bolin Zhu[a], Jianchun Li[a], Xin Hu[a], Zinan Zhao[a], Wenfeng Xu[a], Yang Jv[e], Dandan Wang[e], Yingming Zheng[c], Yiwen Dong[c], Lu Li[d], Shilei Yang[d], Zhiyuan Teng[f], Ling Lu[f], Jingwei Zhu[f], Linzhe Du[b], Yunxin Liu[b], Lechuan Jia[g], Qiujv Zhang[g], Hui Ma[g], Ana Zhao[h], Hongliu Jiang[h], Xin Xu[i], Jinli Wang[i], Xuping Qian[i], Wei Zhang[j], Tingting Zheng[j], Chunxia Yang[k], Xuguang Chen[k], Kun Liu[l], Huanhuan Jiang[l], Dongxiang Qu[m], Jia Song[m], Hua Cheng[n], Wenfang Sun[n], Hanqiu Zhan[o], Xiao Li[o], Yafeng Wang[p], Aixia Wang[p], Li Liu[q], Lihua Yang[q], Nan Zhang[r], Shumin Chen[s], Jingjing Ma[t], Wei Liu[u], Xiaoxiang Du[v], Meiqin Zheng[w], Liyan Wan[x], Guangqing Du[y], Hangmei Liu[z], Pengfei Jin[a,*]**

[a]*Department of Pharmacy, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing Key Laboratory of Assessment of Clinical Drugs Risk and Individual Application (Beijing Hospital), Beijing 100730, China*
[b]*Department of Pharmacy, Nanjing First Hospital, Nanjing Medical University, Nanjing 210006, China*
[c]*Department of Pharmacy, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China*
[d]*Department of Pharmacy, First Affiliated Hospital of Dalian Medical University, Dalian 116011, China*
[e]*Department of Respiratory and Critical Care Medicine, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing 100730, China*

*Corresponding author.
E-mail address: j790101@163.com (Pengfei Jin).

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[†]These authors made equal contributions to this work.

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[f]*Department of Pharmacy, the Second People's Hospital of Guiyang (Jinyang Hospital)/the Affiliated Jinyang Hospital of Guizhou Medical University, Guiyang 550023, China*
[g]*Department of Pharmacy, General Hospital of Ningxia Medical University, Yinchuan 750004, China*
[h]*Department of Pharmacy, Changchun Central Hospital, Changchun 130051, China*
[i]*Department of Pharmacy, Affiliated Hospital of Nantong University, Nantong 226001, China*
[j]*Department of Pharmacy, Beijing Jishuitan Hospital, Capital Medical University, Beijing 100035, China*
[k]*Department of Pharmacy, Beijing Shunyi Hospital, Beijing 101300, China*
[l]*Department of Pharmacy, North China University of Science and Technology Affiliated Hospital, Tangshan 063000, China*
[m]*Department of Pharmacy, the First Hospital of Qiqihar, Qiqihar 161005, China*
[n]*Department of Pharmacy, Beijing Luhe Hospital, Capital Medical University, Beijing 101100, China*
[o]*Department of Pharmacy, Beijing Ditan Hospital, Capital Medical University, Beijing 100015, China*
[p]*Department of Pharmacy, Qinghai Provincial People's Hospital, Xining 810007, China*
[q]*Department of Pharmacy, the Fifth People's Hospital of Ningxia, Shizuishan 753000, China*
[r]*Department of Pharmacy, Beijing Chuiyangliu Hospital, Beijing 100022, China*
[s]*Department of Pharmacy, Fuxing Hospital, Capital Medical University, Beijing 100038, China*
[t]*Department of Pharmacy, the Fourth Affiliated Hospital of Soochow University, Suzhou Dushu Lake Hospital, Medical Center of Soochow University, Suzhou 215000, China*
[u]*Department of Pharmacy, Beijing YouAn Hospital, Capital Medical University, Beijing 100069, China*
[v]*Department of Pharmacy, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China*
[w]*Department of Pharmacy, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing 101149, China*
[x]*Department of Pharmacy, the First Hospital of Tsinghua University, Beijing 100016, China*
[y]*Department of Pharmacy, Beijing Rehabilitation Hospital Affiliated to Capital Medical University, Beijing 100144, China*
[z]*Department of Pharmacy, Emergency General Hospital, Beijing 100028, China*

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**Abstract** Debates persist regarding the efficacy and safety of azvudine, particularly its real-world outcomes. This study involved patients aged ≥60 years who were admitted to 25 hospitals in mainland China with confirmed SARS-CoV-2 infection between December 1, 2022, and February 28, 2023. Efficacy outcomes were all-cause mortality during hospitalization, the proportion of patients discharged with recovery, time to nucleic acid-negative conversion ($T_{NANC}$), time to symptom improvement ($T_{SI}$), and time of hospital stay ($T_{HS}$). Safety was also assessed. Among the 5884 participants identified, 1999 received azvudine, and 1999 matched controls were included after exclusion and propensity score matching. Azvudine recipients exhibited lower all-cause mortality compared with controls in the overall population (13.3% *vs*. 17.1%, RR, 0.78; 95% CI, 0.67−0.90; $P = 0.001$) and in the severe subgroup (25.7% *vs*. 33.7%; RR, 0.76; 95% CI, 0.66−0.88; $P < 0.001$). A higher proportion of patients discharged with recovery, and a shorter $T_{NANC}$ were associated with azvudine recipients, especially in the severe subgroup. The incidence of adverse events in azvudine recipients was comparable to that in the control group (2.3% *vs*. 1.7%, $P = 0.170$). In conclusion, azvudine showed efficacy and safety in older patients hospitalized with COVID-19 during the SARS-CoV-2 omicron wave in China.



## 1. Introduction

During the transitional period from late 2022 to early 2023, the world witnessed a remarkable upsurge in cases of coronavirus disease 2019 (COVID-19) due to the emergence of the omicron variant, which spurred a global response[1-3]. To combat this outbreak, azvudine has been widely administered[4]. Azvudine is the first domestically produced oral anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) agent in China. Its evaluation as a potential COVID-19 treatment commenced after its successful clinical application against human immunodeficiency virus (HIV)-1 infection[5].

To evaluate the therapeutic potential of azvudine against mild-to-moderate COVID-19, a series of clinical trials have been conducted in China, Russia, and Brazil[6-8]. These pivotal trials included 348 patients in China, 314 in Russia, and 453 in Brazil. The results showed significantly lower viral load, time to nucleic acid-negative conversion ($T_{NANC}$), and risk of disease progression in the azvudine group compared with the control group.

Based on these promising findings, the National Medical Products Administration in Beijing, China, provisionally authorized the use of azvudine for COVID-19 treatment on July 25, 2022[9]. Following the approval of nirmatrelvir/lopinavir, azvudine became the second small-molecule oral medication for COVID-19 in mainland China. The Chinese treatment guidelines on August 9, 2022, prioritized the use of azvudine for treating adult patients with moderate COVID-19[10]. Subsequently, it was added to the medical reimbursement list on August 12, 2022. Timeline for azvudine rollout in China is described in Supporting Information (Appendix 1).

Despite the widespread use of azvudine, its efficacy and safety have been debated. Concerns have been raised regarding the generalizability and credibility of the clinical trials. Moreover, real-world studies have also yielded conflicting results. A study by researchers from Xiangya Hospital indicated a reduced risk of composite disease progression among azvudine recipients; however, no significant variance was observed in overall mortality rates[11]. Conversely, another study by the same group suggested that azvudine was associated with a decreased all-cause mortality rate, even when compared with nirmatrelvir/ritonavir[12]. Moreover, the safety of azvudine remains unclear. Based on five randomized clinical trials, a meta-analysis on the safety of azvudine indicated that the safety of azvudine was better than that in the control group (adverse events: Risk ratios [RR], 0.89; 95% confidence interval [CI], 0.80−0.99; $P = 0.04$)[13]. In another real-world study, a higher incidence of adverse events was observed in those who received azvudine than in those who only received supportive therapy (25.87% *vs*. 8.83%, $P < 0.001$)[14]. Few studies have investigated the effects of azvudine on liver and kidney functions. Debates persist regarding the efficacy and safety of azvudine, particularly its real-world outcomes.

Older individuals face a higher risk of severe illness after infection[15]. Data from the World Health Organization as of January 2023 revealed that COVID-19-related mortality rates were 0.7%, approximately 1.8%, and 3.5% for those aged 60−69, 70−79, and ≥80 years, respectively[16]. In China, >90% of COVID-19-related deaths have been observed in patients with underlying health conditions, particularly older patients with multiple comorbidities[17].

Given the current lack of large-scale clinical studies evaluating the efficacy and safety of azvudine in older patients in real-world settings, this retrospective cohort study aimed to address this gap by analyzing the outcomes of hospitalized older patients infected with the SARS-CoV-2 omicron variant, providing valuable insights into antiviral treatments.

## 2. Methods

### 2.1. Study design

This study used a multicenter, retrospective cohort design to evaluate the efficacy and safety of azvudine in older patients with COVID-19 during hospitalization. Data were collected from 25 hospitals across China. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Hospital (approval number: 2023BJYYEC-031-01), which granted a complete waiver of consent owing to the anonymized patient data and retrospective nature of this study. This study was registered with the China Clinical Trial Registration Center (No. ChiCTR2300072750) and China Medical Research Registration System (No. MR-11-23-025839). The study protocol is described in Supporting Information (Appendix 2).

### 2.2. Data sources and study population

The study cohort comprised individuals aged ≥60 years who tested positive for SARS-CoV-2 infection (confirmed by reverse transcription-polymerase chain reaction or rapid antigen test) and were admitted to the hospitals between December 1, 2022, and February 28, 2023. The exclusion criteria were as follows: (1) use of other antiviral agents within the 2 weeks before admission; (2) absence of crucial data, such as COVID-19 severity, symptom onset time, and SARS-CoV-2 testing results; and (3) azvudine or supportive treatment for <72 h.

The investigators obtained patient characteristics and outcomes from the physical or electronic medical records of each center. Data collected included demographic information (age, sex, weight, body mass index [BMI], admission date, comorbidities, date of discharge or death), details of azvudine exposure (timing, dosage, duration, and co-medications), COVID-19 severity upon admission, $T_{NANC}$, time to symptom improvement ($T_{SI}$), time of hospital stay ($T_{HS}$), and laboratory test results. These results included liver function parameters (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), renal function parameters (blood urea nitrogen [BUN], serum creatinine [SCR], estimated glomerular filtration rate [eGFR]), and serum albumin (ALB). Baseline data were extracted before azvudine or supportive treatment applied.

### 2.3. Variable definitions

Patients with COVID-19 were classified as having mild, moderate, or severe disease. The severity of COVID-19 aligned with the Chinese Diagnosis and Treatment Protocol for COVID-19 (version 10)[18]. In this study, both severe and critical COVID-19 subtypes were categorized as severe COVID-19. Detailed criteria for COVID-19 severity are provided in Appendix 2.

Patients who received azvudine treatment with or without supportive care during the study period were categorized into the azvudine group, whereas those who received supportive treatment only were assigned to the control group. The comorbidities included diabetes mellitus; hypertension; liver, chronic lung, chronic heart, chronic kidney, chronic neurological diseases; malignancy; and other conditions.

### 2.4. Procedures

Data on patient characteristics, drug exposure, laboratory parameters, COVID-19 severity, symptoms, SARS-CoV-2 test results, and clinical outcomes were collected during hospitalization. The study investigators retrieved research data from physical or electronic medical records at each subcenter and subsequently forwarded them to the central hub of Beijing Hospital.

To ensure data quality and reliability, researchers at Beijing Hospital performed thorough quality control screening of all data.

This rigorous screening process aims to incorporate only precise and reliable data into the study.

To address potential confounding factors, logistic regression was used to estimate the propensity score, with treatment status as the dependent variable and age, sex, and COVID-19 severity as the independent variables. Propensity score matching (PSM) was performed at a 1:1 ratio without replacement. Each individual in the azvudine group was matched with an individual in the control group with the most similar propensity score. This process ensured the quality of the matching results by setting a caliper value of 0.2. Subsequently, changes in the standard difference of covariates between the groups were compared before and after matching. The closer the standard differences are to 0, the more satisfactory the matching results. An absolute value of standard differences below 0.1 indicates a favorable balance of intergroup variables after matching.

### 2.5. Outcomes

The primary efficacy outcome was all-cause mortality during hospitalization, whereas the secondary outcomes included the proportion of patients discharged with recovery, $T_{NANC}$, $T_{SI}$, and $T_{HS}$ Recovery was defined as follows: considerable improvement in respiratory symptoms, evident absorption of inflammation on pulmonary imaging, negative respiratory pathogen nucleic acid tests, and normal temperature maintained for >24 h. Discharge against medical advice (DAMA) pertains to a subset of patients who are neither dead nor fully recovered but choose to leave against the discharge criteria and the advice of healthcare providers. $T_{SI}$ was defined as the time from symptom onset to any reduction in COVID-19 symptoms at baseline[19]. The participants were monitored from admission until discharge or death.

The primary safety outcome was the incidence of adverse events, whereas the secondary safety outcomes were the effects of azvudine on hepatic function (ALT, AST), renal function (BUN, SCR, eGFR), and ALB. Severe adverse events were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, in which grades 3−5 were considered severe[20].

### 2.6. Statistical analyses

Detailed sample size calculations and statistical analyses are provided in Appendix 2. The sample size was calculated based on the results of these two studies. Yang et al.[14] revealed disease progression rates of 1.27% and 2.87% in the azvudine and control groups, respectively, on Day 28. To achieve a significance level of 5% and a power of 80%, a minimum of 1550 participants in each group was determined[14]. Chen et al.[21] reported a mean difference of −1.658 days (95% CI, −2.772 to −0.544) in $T_{NANC}$ between the azvudine and control groups. Based on this analysis, an estimated minimum of 480 participants per group was required to achieve a power of approximately 80% and a significance level of 5%. Consequently, the study aimed to enroll at least 1550 participants in each group. Ultimately, 3998 participants were included, meeting the sample size criteria.

The PSM process was performed using the MatchIt package in R (version 4.3.2). We assessed the baseline covariate balance between the groups before and after PSM using the standardized mean difference (SMD), with a value $> 0.1$ indicating covariate imbalance, caliper value $= 0.2$[22].

RRs with 95% CIs for all-cause mortality during hospitalization and incidence of adverse events between azvudine recipients and non-recipients were calculated. The statistical tests for these comparisons were conducted using the Pearson $\chi^2$ test or Fisher's exact test. The mean differences in $T_{NANC}$, $T_{SI}$, $T_{HS}$, and laboratory parameters were assessed using either the *t*-test or Wilcoxon rank-sum test. All statistical analyses were performed using R (version 4.3.2). All significance tests were two-tailed, and a *P*-value <0.05 was considered statistically significant.

## 3. Results

### 3.1. Demographic analysis

In total, 5884 participants were identified from 25 subcenters, with 1472 excluded for not meeting the eligibility criteria. The retrospective cohort comprised 2006 azvudine users and 2406 controls (Fig. 1). The baseline characteristics of the azvudine and control groups before and after 1:1 PSM are shown in Table 1. After matching, 1999 azvudine recipients and their equivalent matched controls were included, demonstrating a significant overlap in propensity score distributions between the two groups (Supporting Information Fig. S1). Baseline characteristics remained well-balanced after matching, with SMDs consistently <0.1. In the original cohort, there was a significantly higher proportion of severe cases in the azvudine group compared with the control group (45.2% *vs*. 38.4%, $P < 0.001$). However, following PSM, no significant differences were observed in terms of mean age, sex distribution, COVID-19 severity, BMI, comorbidities, or laboratory test results between the two groups (Table 1).

### 3.2. Efficacy

Azvudine treatment showed significantly lower odds of all-cause mortality during hospitalization in both the overall population (13.3% *vs.* 17.1%; RR, 0.78; 95% CI, 0.67−0.90; $P = 0.001$) and severe subgroup (25.7% *vs*. 33.7%; RR, 0.76; 95% CI, 0.66−0.88; $P < 0.001$). However, no significant reduction in all-cause mortality during hospitalization was observed in the mild and moderate subgroups (Table 2). All-cause mortality during hospitalization in the original and matched cohorts was provided in Supporting Information Fig. S2.

Similarly, consistent results were observed for the secondary outcomes. Azvudine treatment led to a significantly higher proportion of patients being discharged with recovery (83.8% *vs*. 81.4%; RR, 1.03; 95% CI, 1.00−1.05; $P = 0.041$), particularly in the severe subgroup (69.7% *vs*. 64.4%; RR, 1.08; 95% CI, 1.01−1.15; $P = 0.016$) (Table 2).

The DAMA rates were 2.9% (58/1999) and 1.6% (31/1999) in the azvudine and control groups, respectively.

The results also indicated that participants treated with azvudine had reduced $T_{NANC}$ by 1.5 days in the overall population (12.9 ± 6.6 *vs*. 14.4 ± 9.5 days, $P < 0.001$) and 3.0 days in the severe subgroup (13.0 ± 7.0 *vs*. 16.0 ± 10.5 days, $P < 0.001$). There were no significant differences observed in $T_{SI}$ (15.7 ± 7.4 *vs*. 15.7 ± 9.8 days, $P = 0.873$) or $T_{HS}$ (13.8 ± 6.2 *vs*. 14.0 ± 8.2 days, $P = 0.664$) (Table 3). Survival analysis in $T_{NANC}$ and $T_{SI}$ were provided in Supporting Information Table S1.

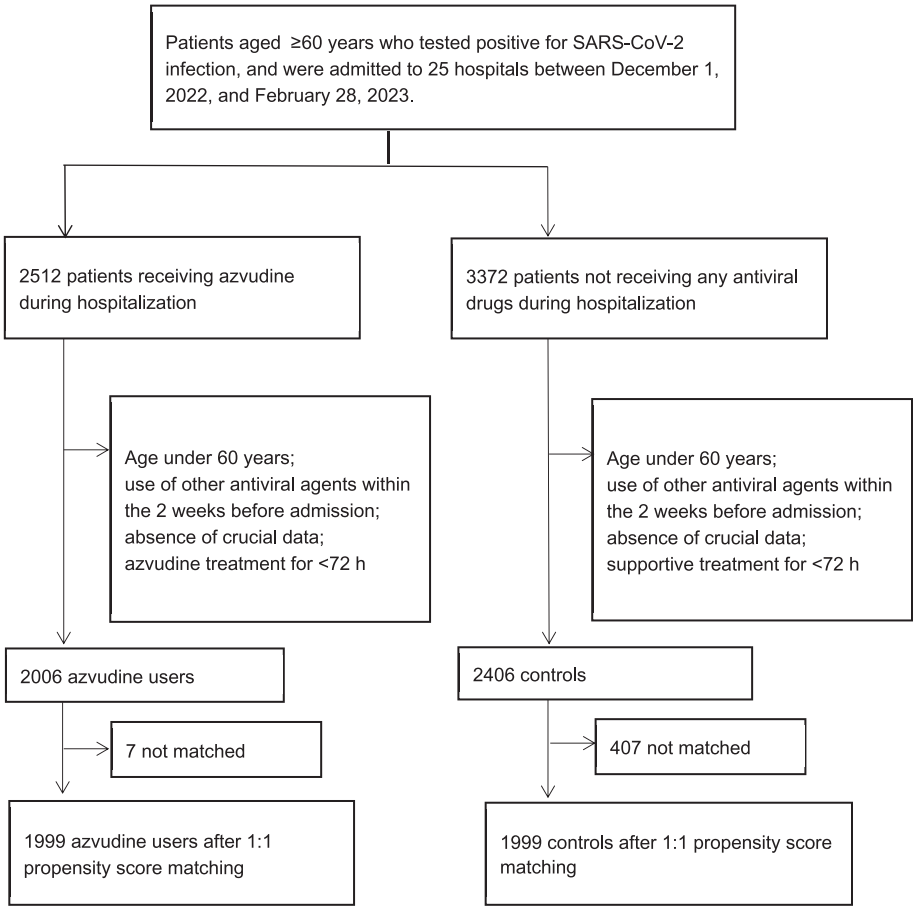


**Figure 1** Study profile.

### *3.3. Safety*

Similar incidences of adverse events were observed in both groups (2.3% *vs*. 1.7%, $P = 0.170$) (Table 4). Gastrointestinal disorders were the most frequently reported adverse events in both groups, with a higher rate observed in the azvudine group than in the control group (1.1% *vs*. 0.4%; RR, 3.00; 95% CI, 1.28−7.04, $P = 0.008$). Importantly, no serious adverse events were reported during the study in either group.

Most laboratory test parameters remained stable after the treatment. After treatment, ALT levels were higher in the azvudine group than in the control group (ΔALT: 1.0 *vs*. −1.0, $P < 0.001$), whereas ALB levels were lower in the azvudine group than in the control group (ΔALB: −1.9 *vs*. −1.2, $P < 0.001$). There were no significant differences in AST levels, BUN levels, or eGFR between the two groups after treatment.

## 4. Discussion

This study aimed to assess the efficacy and safety of azvudine in a retrospective cohort of patients with COVID-19 aged ≥60 years. To our knowledge, this was the first large real-world investigation to examine the inpatient use of azvudine during an omicron variant-dominated pandemic. The findings revealed that azvudine was significantly associated with lower all-cause mortality during hospitalization, a higher proportion of patients discharged with recovery, and shorter $T_{NANC}$. The group receiving azvudine did not exhibit a higher incidence of adverse events compared with the control group, and most laboratory indicators remained stable throughout the treatment. In summary, these results demonstrated the clinical efficacy and safety of azvudine in hospitalized older patients with COVID-19 in China during the omicron wave from late 2022 to early 2023.

Currently, two primary categories of small-molecule antiviral drugs are used to treat COVID-19. The first category comprises protease inhibitors targeting SARS-CoV-2's main proteases, 3CLpro, such as nirmatrelvir/lopinavir, simnotrelvir/lopinavir, ensitrelvir, and leritrelvir. The second category includes RNA-dependent RNA polymerase (RdRp) inhibitors like remdesivir, molnupiravir, azvudine, and remidvir deuterium hydrobromide[23]. Azvudine inhibits the nucleoside reverse transcriptase and restores cytidine deaminase expression[24]. Its broad-spectrum antiviral effects against HIV and hepatitises B and C have been well-established[4,25,26]. Azvudine is converted into active nucleoside triphosphates through kinase catalysis and subsequently incorporated into viral RNA during synthesis, resulting in the prevention of nucleotides addition to the 3′-hydroxyl terminus and inhibition of RNA chain synthesis[27]. Additionally, azvudine notably inhibits viral RdRp activity, resulting in the termination of reverse transcription and suppression of viral replication[25,26]. Azvudine and its metabolites are concentrated in the thymus and peripheral blood monocytes, indicating their immune targeting properties.

Global clinical trials on azvudine have been controversial for various reasons[6-9]. These trials predominantly included mild-to-

**Table 1** Baseline characteristics of the azvudine and control groups.

| Baseline characteristics | Before matching | | | | After 1:1 propensity score matching | | | |
|---|---|---|---|---|---|---|---|---|
| | Azvudine ($n$ = 2006) | Control ($n$ = 2406) | SMD | *P-value* | Azvudine ($n$ = 1999) | Control ($n$ = 1999) | SMD | *P-value* |
| Age | 77.1 (8.8) | 77.4 (9.0) | 0.033 | 0.278 | 77.1 (8.8) | 77.41 (8.8) | 0.036 | 0.253 |
| Sex | | | 0.003 | 0.947 | | | 0.022 | 0.515 |
| Male | 1231 (61.4) | 1473 (61.2) | | | 1226 (61.3) | 1247 (62.4) | | |
| Female | 775 (38.6) | 933 (38.8) | | | 773 (38.7) | 752 (37.6) | | |
| Severity at admission | | | 0.180 | <0.001 | | | 0.002 | 0.999 |
| Mild | 284 (14.2) | 485 (20.2) | | | 278 (13.9) | 279 (14.0) | | |
| Moderate | 816 (40.7) | 998 (41.5) | | | 816 (40.8) | 815 (40.8) | | |
| Severe[a] | 906 (45.2) | 923 (38.4) | | | 905 (45.3) | 905 (45.2) | | |
| BMI, kg/m$^2$[b] | 24.2 (3.9) | 24.0 (4.1) | 0.070 | 0.059 | 24.2 (3.9) | 24.0 (4.1) | 0.056 | 0.152 |
| With comorbidities | 1936 (96.5) | 2336 (97.1) | 0.033 | 0.313 | 1926 (96.3) | 1942 (97.1) | 0.037 | 0.279 |
| Laboratory tests | | | | | | | | |
| ALT[c], U/L | 22.0 (15.0, 34.9) | 21.0 (14.0, 36.0) | 0.075 | 0.225 | 22.0 (15.0, 35.0) | 21.0 (14.0, 36.0) | 0.075 | 0.225 |
| Normal (≤40) | 1539 (81.0) | 1801 (78.8) | | | 1532 (80.9) | 1498 (79.0) | | |
| Abnormal (>40) | 361 (19.0) | 485 (21.2) | 0.055 | 0.082 | 361 (19.1) | 399 (21.0) | 0.049 | 0.142 |
| AST[d], U/L | 29.6 (21.0, 42.5) | 28.0 (20.0, 43.0) | 0.080 | 0.052 | 29.5 (21.0, 42.5) | 28 (20.0, 43.0) | 0.088 | 0.052 |
| Normal (≤35) | 1201 (63.7) | 1453 (65.2) | | | 1195 (63.7) | 1218 (65.2) | | |
| Abnormal (>35) | 683 (36.3) | 777 (34.8) | 0.029 | 0.363 | 682 (36.3) | 650 (34.8) | 0.032 | 0.343 |
| BUN[e], mmol/L | 8.5 (6.6) | 9.3 (7.5) | 0.116 | <0.001 | 8.5 (6.6) | 9.4 (7.5) | 0.134 | <0.001 |
| Normal (≤8.2) | 1219 (66.1) | 1221 (63.9) | | | 1214 (66.1) | 1022 (62.9) | | |
| Abnormal (>8.2) | 626 (33.9) | 689 (36.1) | 0.045 | 0.179 | 624 (33.9) | 602 (37.1) | 0.065 | 0.060 |
| eGFR[f], mL/min/1.73 m$^2$ | 91.0 (44.0) | 89.6 (52.5) | 0.028 | 0.376 | 91.0 (44.0) | 88.8 (53.8) | 0.044 | 0.183 |
| Normal (≥90) | 942 (50.5) | 1065 (48.8) | | | 939 (50.6) | 876 (47.9) | | |
| Abnormal (<90) | 922 (49.5) | 1116 (51.2) | 0.034 | 0.294 | 918 (49.4) | 951 (52.1) | 0.052 | 0.120 |
| ALB[g], g/L | 33.7 (5.1) | 33.6 (5.4) | 0.013 | 0.692 | 33.7 (5.1) | 33.6 (5.4) | 0.020 | 0.542 |
| Normal (≥35) | 890 (47.7) | 1047 (47.9) | | | 885 (47.6) | 866 (47.8) | | |
| Abnormal (<35) | 977 (52.3) | 1138 (52.1) | 0.005 | 0.900 | 975 (52.4) | 945 (52.2) | 0.005 | 0.911 |

Note: Data are presented as mean (standard deviations), $n$ (%), or medians (interquartile ranges). SMD, standardized mean difference; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; SCR, serum creatinine; eGFR, estimated glomerular filtration rate; ALB, serum albumin.

[a]According to classification method of COVID-19 in Chinese Diagnosis and Treatment Protocol for COVID-19 (version 10), there were 230 critical patients in the azvudine group and 187 in the control group before and after matching. These patients were classified under the severe subtype category.

[b]$n$ = 1268 and 1262 for the azvudine groups before and after matching, respectively, and $n$ = 1705 and 1380 for the control groups before and after matching, respectively.

[c]$n$ = 1900 and 1893 for the azvudine groups before and after matching, respectively, and $n$ = 2286 and 1897 for the control groups before and after matching, respectively.

[d]$n$ = 1884 and 1877 for the azvudine groups before and after matching, respectively, and $n$ = 2230 and 1868 for the control groups before and after matching, respectively.

[e]$n$ = 1845 and 1838 for the azvudine groups before and after matching, respectively, and $n$ = 1910 and 1624 for the control groups before and after matching, respectively.

[f]$n$ = 1864 and 1857 for the azvudine groups before and after matching, respectively, and $n$ = 2181 and 1827 for the control groups before and after matching, respectively.

[g]$n$ = 1867 and 1860 for the azvudine groups before and after matching, respectively, and $n$ = 2185 and 1811 for the control groups before and after matching, respectively.

moderate COVID-19 cases, overlooked severe or critical conditions, and were characterized by relatively small sample sizes. The focus of the trials was restricted to nucleic acid conversion or viral load levels, neglecting crucial outcomes. Moreover, the trials were conducted before the emergence of the omicron variant, and the participant pool mainly consisted of younger individuals, lacking representation of the vulnerable older demographic. This study revealed no difference in all-cause mortality between the azvudine and control groups among patients with mild or moderate COVID-19, which is consistent with the self-limiting nature of the disease. A study conducted in Beijing with 804 mild-to-moderate nonhospitalized patients at high risk from December 19, 2022, to January 5, 2023, produced similar findings[13]. These results indicate that azvudine did not reduce all-cause mortality in patients with mild or moderate COVID-19. However, our findings suggested that azvudine was associated with decreased all-cause mortality in severe patients, representing a crucial contribution to existing evidence.

Comparisons of all-cause mortality between azvudine and other antiviral agents were also performed. A real-world direct comparison between azvudine and nirmatrelvir/ritonavir in hospitalized patients showed non-inferiority of azvudine to nirmatrelvir/ritonavir in terms of 28-day mortality (HR 1.41; 95% CI 0.56−3.56; $P$ = 0.471)[28]. Similarly, a retrospective cohort study conducted in China between December 2022 and January 2023 produced comparable results, with no significant differences in in-hospital death events between azvudine and nirmatrelvir/ritonavir recipients[29]. Conversely, a study conducted in Southeast China

**Table 2** Clinical efficacy outcomes for the azvudine and control groups.

| Efficacy outcome | Azvudine[a] | Control[b] | $\chi^2$ | *P*-value | Risk ratio (95% CI) |
|---|---|---|---|---|---|
| All-cause mortality during hospitalization[c] | | | | | |
| Mild | 6 (2.2) | 6 (2.2) | <0.01 | 0.995 | 1.00 (0.33, 3.07) |
| Moderate | 26 (3.2) | 30 (3.7) | 0.30 | 0.583 | 0.87 (0.52, 1.45) |
| Severe[d] | 233 (25.7) | 305 (33.7) | 13.71 | <0.001 | 0.76 (0.66, 0.88) |
| Total | 265 (13.3) | 341 (17.1) | 11.23 | 0.001 | 0.78 (0.67, 0.90) |
| Patients discharged with recovery[e] | | | | | |
| Mild | 263 (94.6) | 272 (97.5) | 3.06 | 0.080 | 0.97 (0.94, 1.00) |
| Moderate | 782 (95.8) | 772 (94.6) | 1.12 | 0.291 | 1.01 (0.99, 1.03) |
| Severe[f] | 631 (69.7) | 583 (64.4) | 5.76 | 0.016 | 1.08 (1.01, 1.15) |
| Total | 1676 (83.8) | 1627 (81.4) | 4.18 | 0.041 | 1.03 (1.00, 1.05) |

Data are presented as *n* (%).

[a]$n$ = 278, 816, and 905 for mild, moderate, and severe subtypes, respectively, in the azvudine group.

[b]$n$ = 279, 815, and 905 for mild, moderate, and severe subtypes, respectively, in the control group.

[c]All-cause mortality during hospitalization in each subgroup = number of deaths in the subgroup/total population of the subgroup.

[d]132 critical patients in the azvudine group and 136 critical patients in the control group were classified into severe subgroup.

[e]Proportion of each subgroup = Number of patients discharged with recovery in the subgroup/total population of the subgroup.

[f]103 critical patients in the azvudine group and 47 critical patients in the control group were classified into severe subgroup.

yielded divergent findings. This study, which included 281 azvudine and 281 nirmatrelvir/ritonavir recipients among patients admitted without the need for oxygen therapy, indicated that azvudine was marginally associated with lower all-cause mortality than nirmatrelvir/ritonavir[12]. Another recently published article showed that neither nirmatrelvir/ritonavir nor azvudine demonstrated a survival benefit in elderly severe patients[30]. These conflicting results may be due to variations in the disease severity and viral variants. In conclusion, the current evidence suggests that azvudine is non-inferior to nirmatrelvir/ritonavir in terms of mortality.

To our knowledge, no previous study has focused on the proportion of patients discharged after azvudine treatment. Our study found no difference between mild and moderate older patients, but found a significant difference in the severe subgroup. $T_{NANC}$ served as an indicator of clinical improvement and efficacy of antiviral drugs, but significantly varied among the studies. In the Phase III clinical trial conducted in Brazil, the $T_{NANC}$ for the azvudine group was 2.72 days shorter in mild patients (5.55 days *vs*. 8.27 days, $P < 0.001$) and 1.15 days shorter in moderate patients (7.73 days *vs.* 8.89 days, $P < 0.001$) compared with the control group[6,8]. In a multicenter observational study involving patients on hemodialysis, $T_{NANC}$ was approximately 8 days shorter in azvudine recipients compared with that in controls[31]. In our study, participants treated with azvudine experienced a 1.5-day reduction of $T_{NANC}$ overall. The prolonged $T_{NANC}$ observed in our study may be attributed to the advanced age of the patients.

Vaccination may represent significant factor influencing efficacy outcomes. As of July/August 2022, 92.3% of Chinese

**Table 3** Other efficacy outcomes for the azvudine and control groups.

| Efficacy outcome | Azvudine[a] ($n$ = 1676) | Control[b] ($n$ = 1623) | *F* | *P*-value |
|---|---|---|---|---|
| $T_{NANC}$, days | | | | |
| Mild | 12.8 (5.9) | 13.7 (8.6) | −1.40 | 0.161 |
| Moderate | 12.8 (6.6) | 13.4 (8.7) | −1.47 | 0.143 |
| Severe | 13.0 (7.0) | 16.0 (10.5) | −5.81 | <0.001 |
| Total | 12.9 (6.6) | 14.4 (9.5) | −5.24 | <0.001 |
| $T_{SI}$, days | | | | |
| Mild | 12.6 (5.4) | 12.9 (8.5) | −0.48 | 0.629 |
| Moderate | 15.5 (6.4) | 15.9 (9.4) | −0.91 | 0.362 |
| Severe | 17.1 (8.7) | 16.8 (10.6) | 0.59 | 0.552 |
| Total | 15.7 (7.4) | 15.7 (9.8) | −0.16 | 0.873 |
| $T_{HS}$, days | | | | |
| Mild | 12.2 (4.9) | 12.3 (6.1) | −0.10 | 0.924 |
| Moderate | 13.1 (5.2) | 13.0 (7.1) | 0.61 | 0.545 |
| Severe | 15.4 (7.3) | 16.1 (9.9) | −1.35 | 0.177 |
| Total | 13.8 (6.2) | 14.0 (8.2) | −0.43 | 0.664 |

Note: Data are presented as means (standard deviations).

$T_{NANC}$, time to nucleic acid-negative conversion; $T_{SI}$, time to symptom improvement; $T_{HS}$, time of hospital stay.

[a]$n$ = 263, 782, and 631 for mild, moderate, and severe subtypes, respectively, in the azvudine group.

[b]$n$ = 272, 772, and 583 for mild, moderate, and severe subtypes, respectively, in the control group.

**Table 4** Safety outcomes for the azvudine and control groups.

| Safety outcome | Azvudine ($n$ = 1999) | Control ($n$ = 1999) | $\chi^2/Z$ | $P$-value | Risk ratio (95% CI) |
|---|---|---|---|---|---|
| Incidences of adverse events | | | | | |
| Gastrointestinal disorders | 21 (1.1) | 7 (0.4) | 7.05 | 0.008 | 3.00 (1.28, 7.04) |
| Liver enzyme elevation | 10 (0.5) | 11 (0.5) | 0.05 | 0.827 | 0.91 (0.39, 2.13) |
| SCR/BUN elevation | 7 (0.4) | 8 (0.4) | 0.07 | 0.796 | 0.88 (0.32, 2.41) |
| Cardiovascular toxicity | 4 (0.2) | 1 (0.1) | NA | 0.375 | 4.00 (0.45, 35.76) |
| Others | 3 (0.2) | 4 (0.2) | NA | 1.000 | 0.75 (0.17, 3.35) |
| Skin rash | 0 (0.0) | 2 (0.1) | NA | 0.500 | NA |
| Total | 45 (2.3) | 33 (1.7) | 1.88 | 0.170 | 1.36 (0.87, 2.13) |
| Changes in laboratory test parameters[a] | | | | | |
| ΔALT[b], U/L | 1.0 (−6.9, 12.0) | −1.0 (−10.0, 10.0) | −4.38 | <0.001 | NA |
| ΔAST[c], U/L | −4.8 (−15.0, 4.0) | −3 (−16.3, 4.4) | 0.69 | 0.490 | NA |
| ΔBUN[d], mmol/L | 0.2 (−1.8, 2.1) | 0.1 (−2.5, 2.2) | −1.46 | 0.144 | NA |
| ΔeGFR[e], mL/min/1.73 $m^2$ | 6.4 (−6.0, 22.1) | 5.7 (−8.2, 21.7) | −1.27 | 0.203 | NA |
| ΔALB[f], g/L | −1.9 (−4.7, 1.1) | −1.2 (−4.4, 2.0) | 3.55 | <0.001 | NA |

Data are presented as $n$ (%) or medians (interquartile ranges).
NA, not applicable; SCR, serum creatinine; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; ALB, albumin.
[a]Data are the subtraction of pre-treatment values from post-treatment values.
[b]$n$ = 1588 for the azvudine group and 1430 for the control group.
[c]$n$ = 1569 for the azvudine group and 1389 for the control group.
[d]$n$ = 1553 for the azvudine groups and 1422 for the control group.
[e]$n$ = 1571 for the azvudine group and 1423 for the control group.
[f]$n$ = 1529 for the azvudine group and 1359 for the control group.

individuals aged 60 years and above had already received at least one dose of the COVID-19 vaccine[32], with this proportion anticipated to increase further by November 2022. Consequently, we did not examine the vaccination status in this study.

Regarding safety evaluation, our study did not find any statistically significant difference in the overall adverse events between the azvudine and control groups, and no serious adverse events were observed in either group, indicating a good safety profile of azvudine for real-world use. Nevertheless, the slightly higher incidence of gastrointestinal disorders, along with the minor increase in ALT levels and decrease in ALB levels among azvudine recipients warrants careful consideration in clinical practice.

This study has inherent limitations associated with retrospective cohort studies. Unmeasured confounding factors may exist, and a definitive causal relationship could not be established. The lack of detailed information regarding comorbidities may limit the generalizability of our findings. This study did not strictly rule out the roles of antimicrobials and traditional Chinese medicine. This study also did not take into account the impact of inflammation on patients. Moreover, a large number of patients were not admitted to hospitals in this COVID-19 rush, which might cause a bias in the results.

## 5. Conclusions

This retrospective cohort study offers valuable real-world evidence supporting the use of azvudine during an omicron wave in hospitalized older patients with COVID-19. These results indicate the efficacy and safety of azvudine treatment, especially in severely ill patients. However, well-designed large-scale randomized controlled trials are required to validate these conclusions.

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## Author contributions

Yuanchao Zhu: Writing − original draft, Conceptualization. Fei Zhao: Data curation. Yubing Zhu: Methodology. Xingang Li: Investigation. Deshi Dong: Methodology. Bolin Zhu: Data curation. Jianchun Li: Data curation. Xin Hu: Investigation. Zinan Zhao: Methodology. Wenfeng Xu: Resources. Yang Jv: Resources. Dandan Wang: Resources. Yingming Zheng: Resources. Yiwen Dong: Resources. Lu Li: Resources. Shilei Yang: Resources. Zhiyuan Teng: Resources. Ling Lu: Resources. Jingwei Zhu: Resources. Linzhe Du: Resources. Yunxin Liu: Resources. Lechuan Jia: Resources. Qiujv Zhang: Resources. Hui Ma: Resources. Ana Zhao: Resources. Hongliu Jiang: Resources. Xin Xu: Resources. Jinli Wang: Resources. Xuping Qian: Resources. Wei Zhang: Resources. Tingting Zheng: Resources. Chunxia Yang: Resources. Xuguang Chen: Resources. Kun Liu: Resources. Huanhuan Jiang: Resources. Dongxiang Qu: Resources. Jia Song: Resources. Hua Cheng: Resources. Wenfang Sun: Resources. Hanqiu Zhan: Resources. Xiao Li: Resources. Yafeng Wang: Resources. Aixia Wang: Resources. Li Liu: Resources. Lihua Yang: Resources. Nan Zhang: Resources. Shumin Chen: Resources. Jingjing Ma: Resources. Wei Liu: Resources. Xiaoxiang Du: Resources. Meiqin Zheng: Resources. Liyan Wan: Resources. Guangqing Du: Resources. Hangmei Liu: Resources. Pengfei Jin: Writing − review & editing, Investigation.

## Conflicts of interest

All researchers can confirm their independence from funders, and all authors, external and internal, had full access to all the data (including statistical reports and tables) in the study and can take

responsibility for the integrity of the data and the accuracy of the data analysis.

National High Level Hospital Clinical Research Funding and National Health Commission Clinical Research Projects for Innovative Drugs had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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## Appendix A. Supporting information

Supporting information to this article can be found online at https://doi.org/10.1016/j.apsb.2024.12.004.

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