BMC Infectious Diseases

RESEARCH

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Association of Azvudine with severe outcomes among hospitalized patients with COVID-19 during an omicron-dominance period in Wuhan, China: a single-center, retrospective, matched cohort study

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Abstract

Background Constantly emerging SARS-CoV-2 genetic variants with potent immune escape kept the COVID-19 pandemic ongoing. Apart from vaccination, effective antiviral drug is necessary to achieve clinical improvement, especially for hospitalized patients. To date, there was limited data on the clinical effectiveness of Azvudine. This study aimed to provide a comprehensive assessment of the effectiveness of Azvudine among hospitalized COVID-19 patients in a real-world healthcare setting.

Method In this single-center, retrospective cohort study, hospitalized patients with laboratory-confirmed SARS-CoV-2 infection from Dec 1, 2022 to May 31, 2023 were recruited in a tertiary hospital in Wuhan, China. Azvudine recipients and controls were propensity-score matched with a ratio of 1:1, based on age, sex, baseline Charlson comorbidity index, time from symptom onset to treatment exposure, initiation of concomitant treatment at admission, and abnormality of chest computed tomography image. The primary outcomes included a composite measure of severe outcomes (ICU admission and invasive mechanical ventilation), and all-cause death, and the secondary outcome was the time to negative nucleic acid conversion. Subgroup analyses were performed according to the matching covariates. The incidence rate was computed, and the hazard ratio (HR) was estimated by using the Cox proportional hazards regression model for each outcome.

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Results A total of 4 979 hospitalized patients (mean age [SD]: 65.4 [20.1] years) with confirmed COVID-19 diagnosis were identified during the study period. After screening and matching, 703 Azvudine recipients, and 703 matched controls were eligible for the primary outcomes, and 201 Azvudine recipients and 201 matched controls were included for the secondary outcome. The median follow-up period was 12 days. The Azvudine users were associated with a significantly lower risk of all-cause death (crude incidence rate: 17.3 per 10 000 person-days [95%CI: 10.6, 28.3] vs. 41.3 per 10 000 person-days [95%CI: 28.4, 52.7]; HR: 0.44 [95%CI: 0.25, 0.78]) and composite sever outcome measure (crude incidence rate: 74.0 per 10 000 person-days [95%CI: 58.0, 94.5] vs. 191.6 per 10 000 person-days [95%CI: 164.6, 222.9]; HR: 0.38 [95%CI: 0.28, 0.51]) than matched controls. Significant protective effectiveness was also observed in ICU admission, and invasive mechanical ventilation. Prescribing Azvudine was also associated with a significantly higher rate of negative nucleic acid conversion (crude incidence rate: 1512.4 per 10 000 person-days [95%CI: 1331.6, 1717.8] vs. 983.8 per 10 000 person-days [95%CI: 862.8, 1121.9]; HR: 1.52 [95%CI: 1.25, 1.86]) than the matched controls. Similar patterns were observed in subgroup analyses.

Conclusion During a SARS-CoV-2 Omicron variants predominant period, initiation of Azvudine could provide considerable protection against all-cause death, composite severe outcome measure, and result in a significantly shorter nucleic acid conversion time among hospitalized patients with COVID-19. A wider use of Azvudine in clinical settings should be considered.

Keywords Azvudine, SARS-CoV-2, Hospitalization, Cohort study

Introduction

The COVID-19 pandemic has led to the development and repurposing of multiple antiviral agents globally for the treatment of SARS-CoV-2 infection. Newly developed agents such as Paxlovid and the repurposed broad-spectrum agents such as remdesivir and molnupiravir have been shown safe and efficacious in clinical trials and granted for clinical use broadly since the earlier phase of the pandemic [1–4]. Numerous subsequent observational studies conducted among different populations have confirmed their real-world effectiveness including improving the disease progression outcomes and facilitating the SARS-CoV-2 RNA clearance [5–9]. In addition, Azvudine, a novel repurposed agent, was found promising in treating patients with COVID-19 [10].

Azvudine is an orally administered nucleoside-based antiviral agent that inhibits the RNA-dependent RNA polymerase (RdRp), which could lead to virus replication inhibition [11]. In an open-label randomized clinical trial, Azvudine users had shorter negative nucleic acid conversion time than standard antiviral treatment users [12]. This finding was also demonstrated by a single-arm clinical trial on compassionate use among moderate and severe patients [13]. Although Azvudine was authorized to be used for treating COVID-19 in China in July 2022, observational clinical studies evaluating its effectiveness in real-world settings remain limited with relatively small sample sizes [14–16]. A previous study has found that Azvudine, compared to standard symptomatic treatment, can reduce the rate of hospitalization and death among mild-to-moderate COVID-19 patients [16]. Previous data have also demonstrated an association between Azvudine and reduced severe outcomes and death among hospitalized COVID-19 patients with pre-existing conditions [14, 15]. However, these studies were questioned as most of the participants received Azvudine long after the symptom onset date (e.g., beyond 5 days after symptom onset), considering that antiviral treatments are normally effective when administered within 5 days of symptom onset [17, 18]. Moreover, whether Azvudine could shorten the nucleic acid conversion time among hospitalized patients remains uninvestigated.

In this retrospective, matched cohort study, we comprehensively evaluated the (post-marketing) clinical effectiveness of Azvudine among hospitalized COVID-19 patients, during an Omicron-dominance period in China, to provide new insights into the clinical use of Azvudine.

Methods

Study design and setting

We conducted a single-center retrospective cohort study in Zhongnan Hospital of Wuhan University, China, comprising patients diagnosed with COVID-19 and admitted to the hospital between December 1, 2022, and May 31, 2023. The waves of COVID-19-related hospitalization appeared from Dec 2022 to late Jan 2023, and in May 2023 (made up of around 95% of all hospitalizations during the study period), consistent with the contemporary outbreaks caused by the Omicron BA.5 and XBB variants in China, respectively [19]. It should be noted that the zero COVID-19 control measures have been gradually lifted in China since late November 2022 [20].

Data source and study participants

We retrieved de-identified electronic health records for hospitalized patients due to COVID-19 from the inpatient system of Zhongnan Hospital of Wuhan University. The SARS-CoV-2 infections were confirmed with

a positive laboratory reverse transcription-polymerase chain reaction (RT-PCR) test results at admission. We collected individual data on demographic characteristics, date of COVID-19 symptom onset, hospital admission, discharge, death, diagnosis, comorbidities, prescription and drug dispensing records, laboratory tests, and chest computed tomography (CT) scans. According to the latest Chinese Diagnosis and Treatment Protocol for COVID-19 (Trial Version ten) issued by the National Health Commission of the People's Republic of China [21], Azvudine was indicated to adult patients with COVID-19 and was not recommended for patients with pregnancy or with severe liver or renal impairment. Patients with COVID-19 had equal accessibility to oral antiviral medications (e.g., Azvudine, Paxlovid, and molnupiravir) without any preferential allocation among them. We excluded patients who were under 18 years old, dead, or admitted to the intensive care unit (ICU) with oxygen support at hospital admission. We also excluded patients with pregnancy, liver or renal transplantation, an estimated glomerular filtration rate (eGFR) below 30 ml/min, hepatocellular carcinoma, a history of prior use of Azvudine or other antiviral agents (including Paxlovid and molnupiravir) before admission, and those with missing symptom onset date, to ensure, as much as possible, that the included study participants have an equal opportunity to receive Azvudine. Eligible patients were consecutively recruited during the study period.

Ethical statement

This study was approved by the Medical Ethics Committee of Zhongnan Hospital of Wuhan University (Reference number: 2023013 K) and was registered in the Chinese Clinical Trial Registry (Registration number: ChiCTR2300072963; registration date: 2023-06-28). Patient-inform consent was waived because anonymized data was used in this study.

Treatment exposure and outcome measures

The exposure group was defined as hospitalized patients with COVID-19 who received the Azvudine and the control group included those who did not receive Azvudine [21]. We considered the therapeutic period as within the 2 days after admission to overcome the immortal time bias between treatment initiation and admission [15, 22]. The study's primary outcomes were a composite measure of severe outcomes (i.e., ICU admission or invasive mechanical ventilation including initiation of endotracheal intubation and machine ventilation) and all-cause death. The secondary outcome was the occurrence of negative nucleic acid conversion and the time to nucleic acid conversion (defined as the duration between the first negative RT-PCR result and the admission). In the analysis for the secondary outcome, we excluded patients who did not undergo follow-up RT-PCR tests after admission. Hospital length of stay was also considered an additional outcome variable analyzed restricted to patients discharged alive. The follow-up period started from the admission till the occurrence of the outcome events or discharge, whichever comes first.

Covariates

Individual data on age, sex, time from symptom onset to treatment exposure, Charlson Comorbidity Index (CCI, calculated based on the individual data on comorbidity, a higher value indicates a higher predicted mortality rate), abnormal chest CT scan image (i.e., typical chest imaging manifestations such as patch shadow, scattered inflammation, infection, and pneumonia, reflects the baseline severity of respiratory system) and concomitant treatment initiated upon admission (i.e., antibiotic drug, systemic steroid, and monoclonal antibody) were retrieved at baseline.

Propensity score matching

We applied 1:1 propensity score matching (PSM) conditional on the aforementioned baseline characteristics, which were chosen based on possible associations with the outcome variables to mitigate the confounding in the intention to receive Azvudine. The propensity score was estimated by a logistic regression model. We used an approach of caliper matching without replacement with a caliper width of 0.05 to estimate the probability of receiving Azvudine. Standardized mean difference (SMD) was used to examine the balance of each baseline covariate between groups before and after PSM. An SMD below 0.1 represents a balance among covariates [23].

Statistical analysis

Baseline characteristics were compared between Azvudine and control groups before and after PSM. To compare the outcomes between groups, the crude incidence rate of outcome events was computed as the number of events per 10,000 person-days. We utilized the Cox proportional hazards (PH) regression model to estimate the hazard ratio (HR) and the corresponding 95% confidence interval (95% CI) for each outcome between Azvudine recipients and non-recipients. The proportional hazards assumption was not violated given the insignificant correlation (with p-value > 0.05) between Schoenfeld residuals and follow-up time. Subgroup analyses were performed for the primary and secondary outcomes by sex, age groups (≤ 65 or > 65 years), abnormal chest CT image (yes or no), systemic steroid use at admission (yes or no), antibiotic drug use at admission (yes or no), CCI categories (0–2 or > 2) and time from symptom onset to treatment (≤ 5 days or > 5 days). Linear regression model was used to estimate the mean difference (MD) and the

corresponding 95%CI of the hospital length of stay, and the time to negative nucleic acid conversion.

All statistical analyses were performed using R statistical software, version 4.0.2 (R Foundation for Statistical Computing).

Results

A total of 4 979 patients (mean age [SD]: 65.4 [20.1]) admitted to Zhongnan Hospital of Wuhan University with confirmed SARS-CoV-2 infection were identified during the study period, of which 2 325 patients including 724 Azvudine users and 1 601 controls were eligible for inclusion in our study, with a median follow-up period of 12 days (Fig.1). There was no missing data on the baseline characteristics. The baseline characteristics for Azvudine and control groups before 1:1 PSM were shown in Table 1. After matching, collectively 703 Azvudine recipients and 703 matched controls were included for primary outcome analysis, with the SMD of each covariate lower than 0.1, indicating a good balance between groups (Table 1). The majority of the patients received Azvudine within 5 days of symptom onset (421, 59.9%) and 662 (94.2%) Azvudine recipients completed the regimen course within a week. Most of the enrolled participants had a higher CCI and an abnormal chest CT scan image (Table 1). After excluding patients without consequent RT-PCR test after admission, in total 901 patients left, and we finally included 201 Azvudine users and 201 controls after PSM for the secondary outcome analysis.

During the observational period, the crude incidence rate of all-cause death (number of deaths was 19) was 17.3 per 10 000 person-days among Azvudine recipients and was 41.3 per 10 000 person-days among matched controls (number of deaths was 42); there were 74 per 10 000 person-days (number of events was 64) and 191.6 per 10 000 person-days (number of events was 164) amongst Azvudine group and control group, respectively, experiencing the composite severe outcomes during follow-up (Table 2). Azvudine was associated with a significantly lower risk of all-cause death (HR: 0.44; 95%CI: 0.25, 0.78) and composite severe outcome (HR: 0.38; 95%CI:

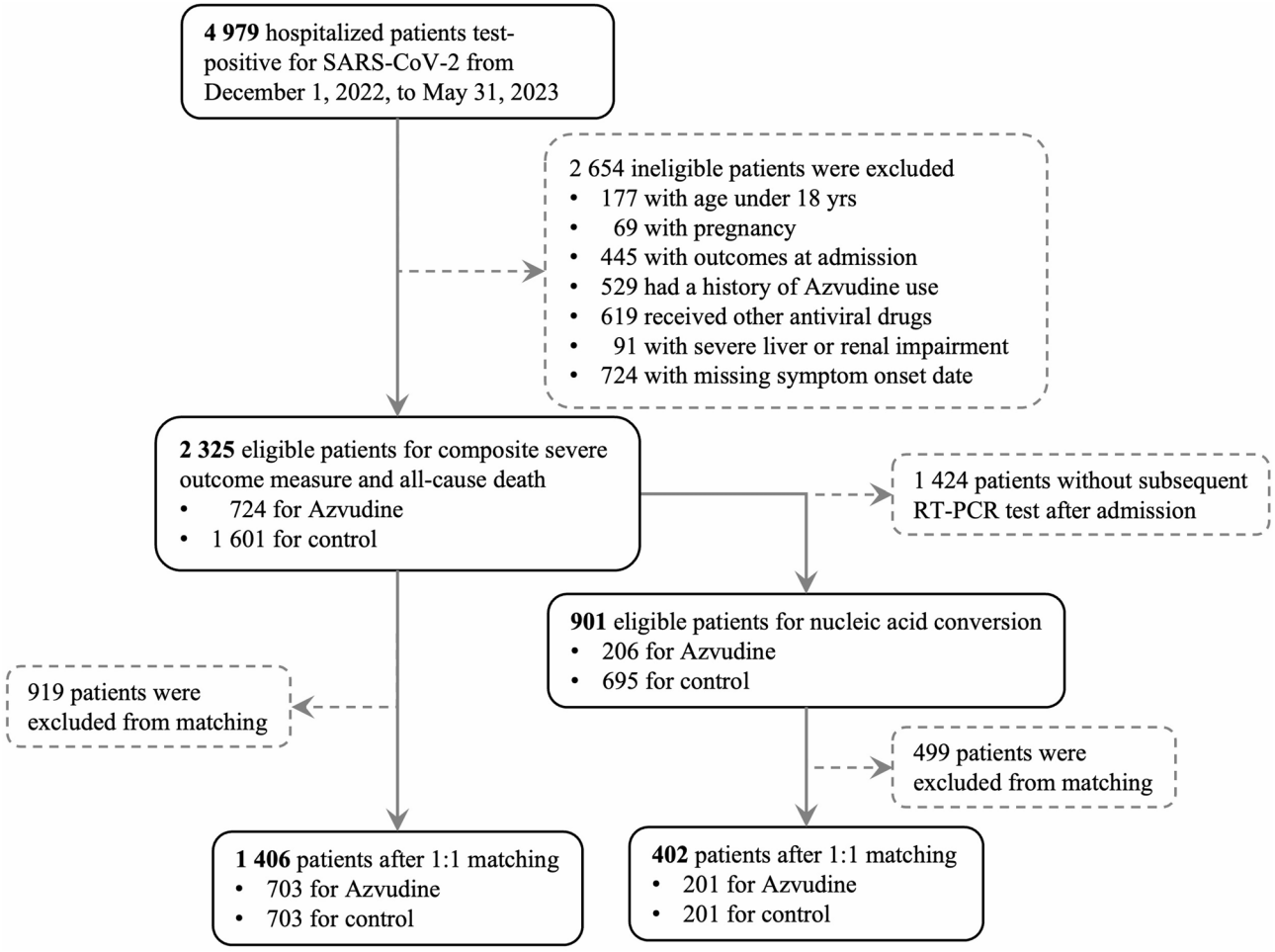

Fig. 1 Flowchart for the identification of eligible Azvudine users and their matched controls for all-cause death and composite severe outcome measure (primary outcome) and negative nucleic acid conversion (secondary outcome)

Table 1 Baseline characteristics of included study participants

Baseline characteristics	Before matching		SMD	After matching		SMD
	Azvudine (*n* = 724)	Controls (*n* = 1601)		Azvudine (*n* = 703)	Controls (*n* = 703)	
Mean age, yr (SD)	67.6 (13.6)	67.1 (15.9)	0.034	67.3 (13.6)	68.2 (14.8)	0.053
≤ 65, *n* (%)	294 (40.6)	665 (41.5)		293 (41.7)	274 (39.0)	
>65, *n* (%)	430 (59.4)	936 (58.5)		410 (58.3)	429 (61.0)	
Sex, *n* (%)						
Male	414 (57.2)	897 (56.0)	0.023	401 (57.0)	394 (56.0)	0.023
Female	310 (42.8)	704 (44.0)		302 (43.0)	309 (44.0)	
Time since symptom onset, *n* (%)						
≤ 5 days	438 (60.5)	1107 (69.1)	0.282	421 (59.9)	422 (60.0)	0.007
>5 days	286 (39.5)	494 (30.9)		282 (40.1)	281 (40.0)	
Charlson Comorbidity Index, *n* (%)						
0–2	259 (35.8)	552 (34.5)	0.027	257 (36.6)	241 (34.3)	0.036
>2	465 (64.2)	1049 (65.5)		446 (63.4)	462 (65.7)	
Abnormal chest CT, *n* (%)	531 (73.3)	960 (60.0)	0.303	512 (72.8)	530 (75.4)	0.064
Concomitant treatments initiated at admission, *n* (%)						
Antibiotic drug	166 (22.9)	305 (19.1)	0.092	158 (22.5)	150 (21.3)	0.047
Systemic steroid	329 (45.4)	427 (26.7)	0.377	308 (43.8)	295 (42.0)	0.046
Monoclonal antibody	6 (0.8)	9 (0.6)	0.029	5 (0.7)	5 (0.7)	0.000

SMD standardized mean difference, *CT* chest computed tomography

0.28, 0.51) (Table 2; Fig. 2). Additionally, a significantly reduced rate of ICU admission (HR: 0.37; 95%CI: 0.27, 0.50) and initiation of mechanical ventilation (HR: 0.46; 95%CI: 0.25, 0.86) were observed for Azvudine users. For the secondary outcome, the crude incidence rates of negative nucleic acid conversion for Azvudine and control groups were 1512.4 per 10 000 person-days and 983.8 per 10 000 person-days. Prescribing Azvudine was associated with a significantly higher nucleic acid conversion rate (HR: 1.52; 95%CI: 1.25, 1.86) (Table 3; Fig. 2), with significantly shorter mean negative conversion time (Azvudine group: 6.6 days vs. control group: 10.2 days; MD: 3.6 days [95%CI: 1.9, 5.2]). In addition, amongst patients who were discharged alive, the length of hospital stay was significantly shorter for the Azvudine user ($n = 687$, mean of 8.4 days) than for the controls ($n = 661$, mean of 9.5 days), with a MD of 1.1 days (95%CI: 0.4, 1.7).

Subgroup analysis showed a significantly lower risk of all-cause death for the Azvudine group among male patients, patients over the age of 65, patients with abnormal chest CT image, antibiotic drug use at admission, higher CCI (i.e., >2) and patients who received Azvudine 5 days after symptom onset (Table 2). The results remained significant whether using systemic steroids at admission or not. Results regarding the composite severe outcome measure remained significant in favor of using receiving Azvudine for all strata, with the higher effect size observed among patients with lower CCI (i.e., 0–2) (Table 2). Concerning the nucleic acid conversion, insignificant results were found in patients without an abnormal chest CT image and in those who received antibiotic drugs at admission (Table 3).

Discussion

The COVID-19 pandemic is still ongoing and dominated by continuously emerging variants with enhanced immune escape and pathogenicity [24, 25], weakening vaccines' effectiveness against the virus [26, 27]. A demand exists for effective antiviral treatment to prevent death, and severe outcomes, alleviate the viral burden, and accelerate clinical convalescence. In this retrospective cohort study, we found the receipt of Azvudine could significantly lower the risk of composite severe outcome progression and death and gave rise to a faster negative nucleic acid conversion and time to recovery (i.e., hospital length of stay) among hospitalized COVID-19 patients. Our findings complemented the previous evidence with a larger sample size and lent support to the use of Azvudine for hospitalized patients with COVID-19 in real-world clinical settings to prevent severe outcomes.

In this study, a significant risk reduction in all-cause death among Azvudine users was observed, which was mainly driven by patients who received Azvudine within 5 days of their symptom onset (non-significant effect was found for those who received Azvudine 5 days after symptom onset). This finding might not be comparable to an unpublished similar study conducted by Shen et al. [14]., in which the majority of the patients received Azvudine beyond 5 days of symptom onset, and non-significant results were found in the subgroup analyses. Likewise, a previous study conducted among patients with pre-existing conditions by Sun et al.. showed non-significant results against all-cause death (0.45, 95%CI: 0.15, 1.36) [15], which was also largely determined by patients who took Azvudine 5 days after symptom onset.

Table 2 Risks of all-cause death and composite severe outcome measure (primary outcomes) for azvudine recipients and matched controls

	Azvudine ($n=703$)		Controls ($n=703$)		Hazard ratio (95% CI)
	Incidence rate, per 10 000 person-day (95% CI)	Total length of follow-up, person-day	Incidence rate, per 10 000 person-day (95% CI)	Total length of follow-up, person-day	
All-cause death					
Overall	17.3 (10.6, 28.3)	9239	41.3 (28.4, 52.7)	10169	0.44 (0.25, 0.78)
Male	25.9 (15.3, 43.7)	5409	57.5 (41.1, 80.4)	5911	0.46 (0.25, 0.87)
Female	5.2 (1.3, 20.9)	3830	18.8 (9.4, 37.5)	4258	0.31 (0.07, 1.49)
Age ≤ 65 yrs	3.1 (0.4, 22.0)	3221	27.6 (14.4, 52.9)	3265	0.56 (0.31, 1.04)
Age > 65 yrs	24.9 (15.0, 41.3)	6018	47.8 (34.0, 67.2)	6904	0.48 (0.26, 0.89)
Abnormal chest CT image: Yes	10.9 (5.5, 21.8)	7344	31.7 (21.6, 46.6)	8192	0.37 (0.17, 0.81)
Abnormal chest CT image: No	42.2 (21.1, 84.3)	1895	80.9 (49.7, 131.8)	1977	0.49 (0.21, 1.15)
Systemic steroid use at admission: Yes	29.4 (17.1, 50.7)	4415	59.1 (40.6, 86.1)	4565	0.51 (0.26, 0.99)
Systemic steroid use at admission: No	6.2 (2.0, 19.3)	4824	26.8 (16.1, 44.4)	5604	0.24 (0.07, 0.82)
Antibiotic drug use at admission: Yes	19.0 (7.1, 50.6)	2106	48.4 (26.1, 89.7)	2068	0.40 (0.13, 1.28)
Antibiotic drug use at admission: No	16.8 (9.6, 29.6)	7133	39.5 (28.0, 55.8)	8101	0.44 (0.23, 0.86)
Charlson Comorbidity Index: 0–2	18.9 (10.7, 33.3)	6345	10.1 (3.3, 31.3)	2970	0.33 (0.03, 3.21)
Charlson Comorbidity Index: >2	9.9 (3.2, 30.5)	3044	54.5 (35.9, 82.7)	4036	0.47 (0.26, 0.85)
Time since symptom onset > 5 days	15.8 (7.6, 33.2)	4419	36.5 (22.7, 58.7)	4653	0.50 (0.21, 1.20)
Time from symptom onset ≤ 5 days	18.7 (9.7, 35.9)	4820	45.3 (30.7, 67.0)	5516	0.43 (0.20, 0.91)
Composite severe outcome measure					
Overall	74.0 (58.0, 94.5)	8647	191.6 (164.6, 222.9)	8560	0.38 (0.28, 0.51)
Male	86.4 (64.1, 116.3)	4979	227.9 (189.3, 274.4)	4783	0.37 (0.26, 0.53)
Female	57.3 (37.4, 87.7)	3668	145.6 (112.0, 189.3)	3777	0.37 (0.22, 0.62)
Age ≤ 65 yrs	51.7 (31.7, 84.3)	3093	186.0 (141.7, 244.1)	2742	0.27 (0.16, 0.48)
Age > 65 yrs	86.4 (65.2, 114.5)	5554	194.2 (161.8, 233.1)	5818	0.42 (0.30, 0.59)
Abnormal chest CT image: Yes	71.9 (54.4, 95.0)	6817	192.7 (162.7, 228.4)	6797	0.36 (0.26, 0.50)
Abnormal chest CT image: No	82.0 (49.5, 135.7)	1830	187.1 (133.5, 262.4)	1763	0.40 (0.22, 0.74)
Systemic steroid use at admission: Yes	84.6 (60.8, 117.7)	4137	210.6 (169.3, 261.9)	3752	0.40 (0.27, 0.59)
Systemic steroid use at admission: No	64.3 (44.7, 92.4)	4510	176.8 (143.2, 218.3)	4808	0.36 (0.23, 0.54)
Antibiotic drug use at admission: Yes	86.2 (53.7, 138.4)	1972	200.1 (144.2, 277.8)	1749	0.42 (0.24, 0.75)
Antibiotic drug use at admission: No	70.4 (53.0, 93.6)	6675	189.4 (159.6, 224.7)	6811	0.37 (0.26, 0.51)
Charlson Comorbidity Index: 0–2	38.2 (21.2, 69.0)	2876	162.0 (119.6, 219.5)	2531	0.24 (0.12, 0.46)
Charlson Comorbidity Index: >2	91.8 (70.2, 120.1)	5771	204.0 (171.3, 243.0)	6029	0.44 (0.32, 0.61)
Time since symptom onset > 5 days	57.9 (41.0, 81.7)	5530	180.0 (147.2, 220.1)	5167	0.30 (0.20, 0.44)
Time since symptom onset ≤ 5 days	102.7 (72.7, 144.9)	3117	209.3 (166.2, 263.4)	3393	0.46 (0.30, 0.70)

CT chest computed tomography

The 95% CIs were calculated using the Wald method

Although current guidelines did not explicitly indicate the timing for clinical use of Azvudine, timely use of COVID-19 antiviral treatment after symptom onset should preferably be considered to slow disease progression and improve prognosis [21, 28, 29]. Using a larger sample size, our study further demonstrated that Azvudine use within 5 days of symptom onset conferred substantial protection against all-cause mortality and other severe outcomes of COVID-19. Intriguingly, our estimated effectiveness of Azvudine against death was comparable to a Hong Kong study assessing the clinical effectiveness of molnupiravir and Paxlovid among hospitalized COVID-19 patients, in which HR of 0.48 (95%CI: 0.40, 0.59) and 0.34 (95%CI: 0.23, 0.50) were obtained, respectively [9], and comparative studies have demonstrated there was no significant difference between Paxlovid and Azvudine in terms of the clinical benefit against death for COVID-19 hospitalizations [30, 31].

The composite measure of clinical severe outcomes defined in our study, including ICU admission and initiation of machine ventilation, was different from previous relevant studies, where the all-cause death was also included [14, 15] and thus the results might not be directly comparable. Nonetheless, we found that Azvudine recipients had significantly lower rates of ICU admission and initiation of machine ventilation, which were not evident in previous studies using smaller sample sizes [14, 15]. Possible reasons included a larger sample

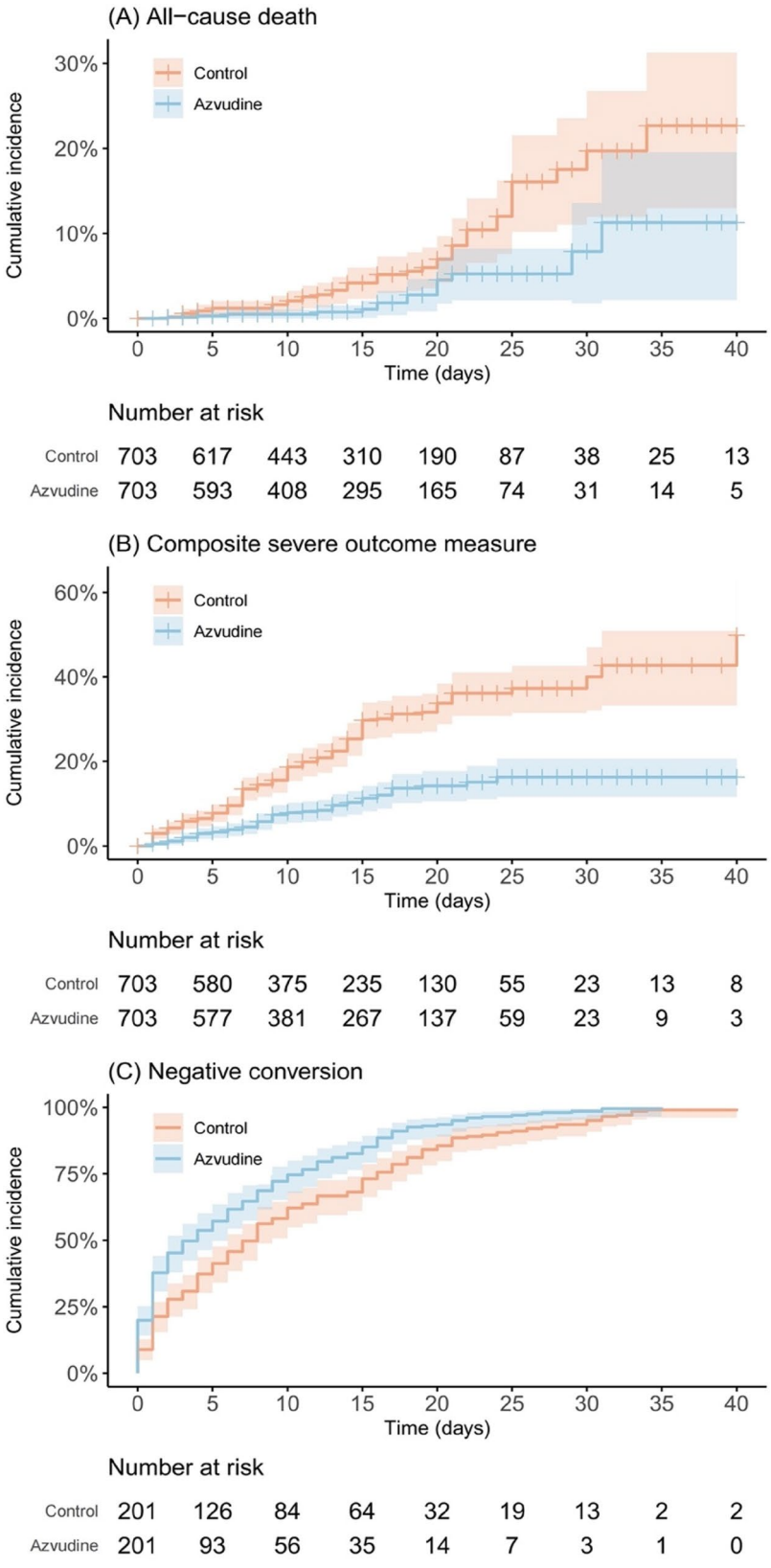

Fig. 2 Cumulative incidence of all-cause death, composite severe outcome measure and negative nucleic acid conversion for Azvudine users and their matched controls. **(A)** All-cause death. **(B)** Composite severe outcome measure. **(C)** Negative nucleic acid conversion. The cross points (i.e., denoted as "+" on the curves) indicated censored observations

Table 3 Time-to-event of negative nucleic acid conversion (secondary outcome) among azvudine recipients and matched controls

	Azvudine ($n=201$)		Controls ($n=201$)		Hazard ratio (95% CI)
	Incidence rate, per 10 000 person-day (95% CI)	Total length of follow-up, person-day	Incidence rate, per 10 000 person-day (95% CI)	Total length of follow-up, person-day	
Overall	1512.4 (1331.6, 1717.8)	1329	983.8 (862.8, 1121.9)	2043	1.52 (1.25, 1.86)
Male	1389.3 (1164.3, 1657.7)	763	947.1 (787.4, 1139.1)	1077	1.46 (1.11, 1.92)
Female	1678.4 (1397.1, 2016.4)	566	1024.8 (850.4, 1235.1)	966	1.64 (1.23, 2.19)
Age ≤ 65 yrs	1658.2 (1383.9, 1986.9)	591	1199.5 (999.0, 1440.3)	842	1.35 (1.02, 1.78)
Age > 65 yrs	1395.7 (1166.8, 1669.5)	738	832.6 (690.2, 1004.5)	1201	1.71 (1.29, 2.27)
Abnormal chest CT image: Yes	1477.3 (1260.5, 1731.3)	880	829.1 (703.2, 977.4)	1568	1.87 (1.45, 2.40)
Abnormal chest CT image: No	1581.3 (1277.4, 1957.5)	449	1494.7 (1206.1, 1852.4)	475	1.05 (0.75, 1.46)
Systemic steroid use at admission: Yes	1350.8 (1081.1, 1687.7)	496	753.8 (591.0, 961.4)	796	1.99 (1.38, 2.86)
Systemic steroid use at admission: No	1608.6 (1377.5, 1878.5)	833	1130.7 (967.9, 1320.9)	1247	1.38 (1.09, 1.75)
Antibiotic drug use at admission: Yes	1273.9 (953.7, 1701.6)	314	1044.0 (772.7, 1410.5)	364	1.23 (0.79, 1.93)
Antibiotic drug use at admission: No	1586.2 (1376.7, 1827.7)	1015	970.8 (839.0, 1123.3)	1679	1.59 (1.28, 1.99)
Charlson comorbidity index: 0–2	1675.3 (1342.0, 2091.3)	388	984.5 (781.9, 1240.6)	660	1.72 (1.21, 2.45)
Charlson comorbidity index: >2	1445.3 (1237.2, 1688.3)	941	983.4 (838.3, 1153.5)	1383	1.46 (1.14, 1.86)
Time since symptom onset > 5 days	595.2 (440.7, 803.9)	672	488.5 (377.5, 632.1)	1126	1.77 (1.16, 2.71)
Time since symptom onset ≤ 5 days	2450.5 (2142.8, 2802.5)	657	1592.1 (1372.1, 1847.5)	917	1.45 (1.15, 1.81)

CT chest computed tomography

The 95% CIs were calculated using the Wald method

size and, on average, earlier receipt of Azvudine among the participants in the present study. Furthermore, our subgroup analyses have shown the robustness of such an effect across various demographic and clinical characteristics, suggesting that Azvudine might be more favorable in preventing severe outcomes compared to other antiviral agents [5, 8, 9]. Specifically, molnupiravir and Paxlovid did not show significant clinical benefit in lowering the risk of severe outcomes among patients aged 65 years or younger [8, 9].

Similar to molnupiravir, Azvudine is a nucleoside analog that inhibits RdRp. In host cells, it is first transformed into active nucleoside triphosphates and then embedded in the SARS-CoV-2 RNA, which would lead to the process of terminating the RNA chain synthesis and virus replication [10, 32]. Moreover, in vivo trials showed that Azvudine exhibited a thymus-homing feature, that is, the Azvudine triphosphates mainly concentrated in the thymus and peripheral blood mononuclear cells, which is a unique feature among existing RdRp inhibitors [13]. The study found that Azvudine could reduce the SARS-CoV-2 viral load and recuperate the thymus, which is the origin site of the T cell that is responsible for the general host immunity against the infection. Our results showed a significantly faster clearance of SARS-CoV-2 RNA (time to negative nucleic acid conversion) among Azvudine recipients, in accord with the findings from early experimental studies for Azvudine [12, 13]. Although a former study indicated a better viral shedding profile favoring faster virus clearance among Paxlovid users than Azvudine users, the time to nucleic acid conversion among Paxlovid users was comparable to the Azvudine users in our study (5.8 versus 6.6 days) [33]. Throughout the COVID-19 pandemic, factors such as aging and comorbidities were associated with reduced T cell immunity in response to infection and more severe outcomes [34, 35], but our findings suggested Azvudine could provide clinical protection among elderly and patients with a higher prevalence of comorbidities.

Our study had several limitations. Firstly, this is an observational study and thus the results could not be interpreted as causations. Moreover, the potential residual confounding such as healthcare seeking behaviour was not considered in the analysis. Secondly, due to limited access to data, we did not have information on the vaccination history of the study participants, which also provided a protective effect against severe outcomes and death. The vaccine uptake may not affect the probability of receiving Azvudine during hospitalization, which was reflected by the sufficiently small SMD of vaccination status between Azvudine treatment and control groups of hospitalized COVID-19 patients reported in another study in China [15]. In addition, the co-variables matched between treatment and control groups may also partly reflect the difference (if any) of the vaccination statuses between the two groups, which were balanced before analysis. However, the clinical effectiveness of Azvudine could be different between vaccinees and non-vaccinees and future investigations are needed for confirmation. Thirdly, patients without abnormal CT findings at admission showed a generally higher incidence rate of severe COVID-19 outcomes than those with abnormal CT findings. This observation might be explained by the fact that patients presenting with more severe respiratory

symptoms typically receive more intensive medical care during hospitalization, potentially reducing their risk of progression to severe outcomes - regardless of Azvudine treatment status. Although this hypothesis could not be verified due to limited data availability, we accounted for abnormal CT findings by including them as a covariate in the PSM process. The matched cohorts demonstrated good balance for this variable. Fourthly, we also did not have access to data on the COVID-19 severity at admission defined by the Chinese Diagnosis and Treatment Protocol for COVID-19. To make the study sample more comparable in terms of the disease severity, we did not include mild cases who were primarily treated in the outpatient setting and critical cases who were directly admitted to the ICU with oxygen support and/or treated with invasive mechanical ventilation at admission and involved chest CT image outcomes and use of concomitant drugs as indicators for COVID-19 severity in propensity score matching. Therefore, our findings may be more generalized to patients with moderate-to-severe COVID-19. Furthermore, the PSM procedure excluded 20 patients over 65 years who received Azvudine. These patients exhibited abnormal CT findings at admission and were initiated on systemic steroids during hospitalization. Their exclusion may introduce selection bias, as this subgroup could represent a clinically distinct population with more severe disease. Lastly, our study participants come from a single center and might not be a representative sample of the general population in China. Nation-wide and multiple-center clinical studies should be conducted in the future.

Conclusion

During a SARS-CoV-2 Omicron variants predominant period, our findings suggested that the use of Azvudine could significantly reduce the risk of death, ICU admission, and use of invasive mechanical ventilation, and resulted in significantly shorter nucleic acid conversion time and hospital length of stay among hospitalized COVID-19 patients. Our study indicated a wider use of Azvudine for improving clinical outcomes should be considered.

Abbreviations

RdRp	RNA-dependent RNA polymerase
RT-PCR	Reverse transcription-polymerase chain reaction
CT	Computed tomography
HR	Hazard ratio
PH	Proportional hazards
SMD	Standardized mean difference
ICU	Intensive care unit
eGFR	Estimated glomerular filtration rate
CCI	Charlson Comorbidity Index
PSM	Propensity score matching
MD	Mean difference

Acknowledgements

We thank healthcare professionals, caregiver partners, and public health practitioners for their contributions to the data and specimen collection.

Clinical trial

This study was registered at the Chinese Clinical Trial Registry (online registration identifier: ChiCTR2300072963; registration date: 2023-06-28).

Authors' contributions

Conceptualization: FS, SZ, and HC. Methodology: ZG and SZ. Software: ZHG. Validation: ZG, WJL, KLW, FS, SZ, and HC. Formal analysis: ZG and SZ. Resources: HC. Data Curation: WL, YL, and SG. Writing - Original Draft: ZG and WL. Writing - Review and Editing: KW, YL, SYG, XPW, YJZ, ZYZ, BQC, FS, SZ, and HC. Visualization: ZG. Supervision: FS, SZ, and HC. All authors critically read the manuscript and gave final approval for publication.

Funding

This work was supported in part by research on technical guidelines for emergency monitoring and evaluation of drugs for the prevention and control of emerging infectious diseases, No.: CST2021CT202, from Chinese Toxicology Association and Efficacy and safety of Qin Fei Pai Du Decoction in the treatment of novel coronavirus disease (COVID-19): a real-world study, No.: ZYYK2021001, From Hubei Provincial Health Commission. SZ was supported by the National Natural Science Foundation of China (grant no.: 12401648, and 72574190), the Noncommunicable Chronic Diseases - National Science and Technology Major Project of China (grant no.: 2023ZD0519300), the Young Elite Scientists Sponsorship (YESS) Program by CAST (grant no.: 24JCQNJC00610), and Tianjin Medical University start-up funding.

Data availability

The original database containing confidential patient information cannot be made publicly available. The anonymized data used in this study may be available based on reasonable request to the corresponding authors.

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Zhongnan Hospital of Wuhan University (No.: 2023013 K). The need for obtaining informed consent to participate was waived by the Medical Ethics Committee of Zhongnan Hospital of Wuhan University. This study adhered to the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 10 April 2025 / Accepted: 3 September 2025
Published online: 14 October 2025

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