

Azvadine reduces the mortality rate of patients with Coronavirus disease 2019: a single-center retrospective analysis study

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Abstract

Background: Several therapeutic drugs have been authorized for the treatment of patients with Coronavirus disease 2019 (COVID-19). However, further research on the mechanisms of action, efficacy, and target populations of these novel therapeutic drugs are necessary. Hence, this study aimed to investigate the effectiveness of azvudine in hospitalized patients with COVID-19.

Methods: We conducted a retrospective cohort study of patients with COVID-19 admitted to our hospital from December 1, 2022, to March 31, 2023. Patients were divided into retrospective cohorts receiving azvudine antiviral therapy and standard treatment, and were followed-up for up to 28 days.

Results: Prior to data processing, azvudine treatment was associated with reduced mortality rates at 7 days (1.09/1000 persons vs. 5.06/1000 persons, $p < 0.001$) and 14 days (3.35/1000 persons vs. 5.65/1000 persons, $p = 0.001$). After propensity score matching, a decrease in mortality rates at 7 days (0.08/1000 persons vs. 6.29/1000 persons, $p < 0.001$), 14 days (3.42/1000 persons vs. 7.26/1000 persons, $p < 0.001$), and 28 days (4.33/1000 persons vs. 7.29/1000 persons, $p = 0.003$) were observed following azvudine treatment. After inverse probability of treatment weighting adjustment, the results were consistent with propensity score matching. In the clinical subgroup analysis, for hospitalized severe and critical patients with COVID-19, azvudine treatment intervention significantly reduced patient mortality rates.

Conclusions: The study suggests that in hospitalized patients with COVID-19, azvudine treatment significantly reduces patient mortality rates in hospitalized COVID-19 infections, wherein the effects are more pronounced in severe and critical patients.

BACKGROUND

The omicron variant of SARS-CoV-2 is causing global havoc, presenting unprecedented challenges to the field of public health.^[1] The rapid spread and extensive impact of this variant have made epidemic prevention and control daunting tasks. In China, the country with the largest population globally, preventive and control measures for COVID-19 are undergoing unprecedented changes. Researchers worldwide are intensifying efforts to develop new therapeutic drugs. Several therapeutic drugs, including Paxlovid, molnupiravir, and azvudine, have been authorized for treating patients with COVID-19.^[2-5] Paxlovid and molnupiravir have shown remarkable performance in clinical trials and real-world populations, effectively reducing the risk of hospitalization and death among patients.^[6, 7] Their mechanism of action mainly involves inhibiting viral replication to alleviate disease symptoms, thereby achieving therapeutic goals.^[6, 7] However, azvudine, China's first oral anti-COVID-19 drug, requires more data to confirm its effectiveness.^[8] Though azvudine has shown some efficacy in small-scale clinical trials, further research is necessary to elucidate its mechanism of action and long-term effects. Similarly, further research on the mechanisms of action, efficacy, and target populations of other novel COVID-19 therapeutic drugs is necessary. Rigorous scientific research is essential to provide patients with safer and

more effective treatment options to overcome this global health crisis. Therefore, this study aimed to investigate the effectiveness of azvudine in hospitalized patients with COVID-19.

METHODS

Study design and participants

This retrospective single-center study was conducted at the First Affiliated Hospital of Gannan Medical University. The study enrolled consecutively diagnosed COVID-19 patients admitted between December 1, 2022, and January 31, 2023, with a 28-day follow-up period. Patients receiving azvudine antiviral therapy formed the azvudine group, while those without antiviral therapy comprised the control group. Patients received standard treatment per the Guidelines for the Diagnosis and Treatment of COVID-19 (Trial 10th edition) from the National Health Commission of the People's Republic of China during hospitalization. Azvudine was orally administered at 5 mg once daily for up to 14 days, with dosage adjustments for renal insufficiency. Institutional Review Board approval was obtained from the First Affiliated Hospital of Gannan Medical University (LLSL-2024065). Patient consent requirement was waived for this retrospective study.

The inclusion criteria were as follows: 1) Patients over 18 years old, regardless of gender; 2) Respiratory samples tested positive for SARS-COV-2 nucleic acid via real-time polymerase chain reaction; and 3) Patients with confirmed COVID-19 cases identified based on diagnostic criteria outlined in the World Health Organization's latest clinical guidelines as of January 28, 2020, or the Guidelines for the Diagnosis and Treatment of COVID-19 (Trial 10th edition) issued by the National Health Commission of the People's Republic of China.

The exclusion criteria were as follows: 1) Patients < 18 years of age; 2) Patients receiving antiviral treatments for human immunodeficiency virus, hepatitis B, hepatitis C, nirmatrelvir-ritonavir, molnupiravir, remdesivir, or Arbidol; 3) Patients with hospital stays < 4 days; 4) Patients receiving azvudine for < 5 days; and 5) Patients with incomplete information.

Data collection

Electronic health records of COVID-19 patients were retrieved from the hospital's database. Information including demographics, admission details, medical history, vaccination status, medication records, nucleic acid diagnosis time, and laboratory tests were gathered. Patients' identification numbers were used to match anonymous vaccination records provided by the Immunization Department of Jiangxi Provincial Center for Disease Control and Prevention. The outcome variable was the all-cause mortality rate at 29 days. Patients were observed from admission to outcome events, discharge, or death. Subsequently, the outcome rate per 1000 person-days was calculated.

Statistical analysis

Continuous quantitative data with a normal distribution were described using mean \pm standard deviation and compared using the t-test. Non-normally distributed data were described using median (P25, P75) and compared using the Mann–Whitney U test. Count data were described using frequency (%), and the comparison between groups was conducted using the chi-square test or Fisher's exact test. Ordinal data were described using frequency (%), and the comparison between groups was conducted using the Mann–Whitney U test. The Kaplan–Meier survival curve analysis and log-rank test were used to compare the differences in mortality rates at different time points between the different treatment groups. Univariate and multivariate Cox regression analyses were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality in the azvudine group relative to the control group. Variables with $p < 0.05$ in the univariate Cox regression analysis were included for adjustment in the multivariate model. We used the MatchIt package in R language for 1:1 propensity score matching (PSM) to control for confounding factors and analyses. The propensity score was calculated using a binary logistic model, with a caliper set at 0.1, and confounding variables included were those with $p < 0.1$ in the univariate Cox regression analysis. For the data after PSM, Kaplan–Meier curves and log-rank tests were used to validate the association between treatment groups and mortality, and the Cox regression models were used to estimate the HRs and 95% CIs. To further compare the differences in mortality rates between treatment groups, we conducted an inverse probability of treatment weighting (IPTW) in R language to control for confounding factors and analyses. The propensity score was calculated using a binary logistic model, and the confounding variables included were the same as those in the previous PSM, which were those with $p < 0.1$ in the univariate Cox regression analysis. For the weighted data, Kaplan–Meier curves and weighted log-rank tests were used to validate the association between groups and the risk of death. Weighted Cox regression models were used to estimate the HRs and 95% CIs. To explore whether the impact of azvudine treatment on prognosis varies among different clinical subtypes, we also conducted analyses according to different clinical subtypes. All statistical analyses and related chart plotting were performed using R language (version 4.3.1). Statistical significance was set at a two-sided $p < 0.05$.

RESULTS

From December 1, 2022, to January 31, 2023, we continuously collected data from 4,077 patients with COVID-19 in our hospital. A total of 2,862 patients were included in this study after exclusion, with 1,372 patients receiving azvudine treatment and another 1,490 patients receiving standard treatment. The flowchart of the entire study process is detailed in Fig. 1. Table 1 displays the baseline demographic and clinical characteristics of the patients. The preliminary data indicate differences in several variables between the two groups. By adjusting variables with $p < 0.05$ in the univariate Cox regression analysis (S1) and conducting 1:1 PSM matching, we ultimately identified data from 920 patients receiving azvudine treatment and 920 patients in the control group for analysis. The baseline characteristics of the two groups remained balanced with a standardized mean difference (SMD) < 0.1 (S2, S4). After IPTW matching, a total of 2,867 azvudine-treated patients and 2,877 patients receiving standard treatment were included, with an SMD < 0.1 (S3, S4).

Table 1
Characteristics of the patients with COVID-19

Variables	Total (n = 2862)	Control group (n = 1372)	Azvodine group(n = 1490)	<i>p</i>
29 days survival,n (%)				0.937
No	2715 (94.9)	1302 (94.9)	1413 (94.8)	
Yes	147 (5.1)	70 (5.1)	77 (5.2)	
Hospital days	10.47 ± 6.43	9.03 ± 6.70	11.79 ± 5.87	< 0.001
Gender, n (%)				< 0.001
Men	1654 (57.8)	715 (52.1)	939 (63)	
Women	1208 (42.2)	657 (47.9)	551 (37)	
Age	65.19 ± 16.99	61.71 ± 18.49	68.41 ± 14.78	< 0.001
BMI	23.17 ± 3.99	23.03 ± 4.15	23.32 ± 3.83	0.137
Cardiovascular diseases,n (%)				0.091
No	2512 (87.8)	1219 (88.8)	1293 (86.8)	
Yes	350 (12.2)	153 (11.2)	197 (13.2)	
Hypertension,n (%)				< 0.001
No	1636 (57.2)	843 (61.4)	793 (53.2)	
Yes	1226 (42.8)	529 (38.6)	697 (46.8)	
Diabetes mellitus,n (%)				< 0.001
No	2269 (79.3)	1138 (82.9)	1131 (75.9)	
Yes	593 (20.7)	234 (17.1)	359 (24.1)	
Chronic kidney disease,n (%)				0.070
No	2538 (88.7)	1232 (89.8)	1306 (87.7)	
Yes	324 (11.3)	140 (10.2)	184 (12.3)	
Chronic obstructive pulmonary disease,n (%)				0.043

Data are n (%) or median (IQ)

Variables	Total (n = 2862)	Control group (n = 1372)	Azvedine group(n = 1490)	p
No	2499 (87.3)	1216 (88.6)	1283 (86.1)	
Yes	363 (12.7)	156 (11.4)	207 (13.9)	
Cancer,n (%)				< 0.001
No	2477 (86.5)	1137 (82.9)	1340 (89.9)	
Yes	385 (13.5)	235 (17.1)	150 (10.1)	
Clinical stages,n (%)				< 0.001
Mild	842 (29.4)	637 (46.4)	205 (13.8)	
Moderate	1585 (55.4)	598 (43.6)	987 (66.2)	
Severe	329 (11.5)	95 (6.9)	234 (15.7)	
Critical	106 (3.7)	42 (3.1)	64 (4.3)	
White blood cells (10 ⁹ /L)	7.10 ± 4.71	7.09 ± 5.20	7.11 ± 4.21	0.920
Red blood cells (10 ¹² /L)	4.08 ± 0.85	4.12 ± 0.86	4.05 ± 0.84	0.033
Hemoglobin (g/L)	120.18 ± 23.76	120.71 ± 23.79	119.69 ± 23.73	0.251
Platelets (10 ⁹ /L)	225.84 ± 107.35	225.57 ± 108.12	226.09 ± 106.68	0.896
Neutrophil (10 ⁹ /L)	5.31 ± 4.39	5.20 ± 4.89	5.41 ± 3.86	0.190
Lymphocyte (10 ⁹ /L)	1.11 ± 0.91	1.17 ± 0.72	1.06 ± 1.05	< 0.001
Monocyte (10 ⁹ /L)	0.60 ± 0.63	0.64 ± 0.80	0.57 ± 0.41	0.009
Eosinophil (10 ⁹ /L)	0.06 ± 0.11	0.07 ± 0.12	0.05 ± 0.10	< 0.001
Basophil (10 ⁹ /L)	0.02 ± 0.03	0.02 ± 0.03	0.01 ± 0.03	< 0.001
Alanine aminotransferase (U/L)	30.34 ± 81.87	29.58 ± 69.49	31.04 ± 91.83	0.629
Aspartate aminotransferase (U/L)	43.30 ± 263.01	48.70 ± 361.29	38.32 ± 112.60	0.308

Data are n (%) or median (IQ)

Variables	Total (n = 2862)	Control group (n = 1372)	Azvodine group(n = 1490)	p
Glutamyl transpeptidase (U/L)	44.63 ± 74.88	43.74 ± 75.19	45.45 ± 74.62	0.542
Alkaline phosphatase (U/L)	82.56 ± 56.86	86.15 ± 66.99	79.25 ± 45.36	0.001
Cholinesterase (U/L)	6090.21 ± 2077.49	6339.82 ± 2121.92	5860.38 ± 2009.19	< 0.001
Total protein (g/L)	62.52 ± 7.25	63.44 ± 7.29	61.68 ± 7.12	< 0.001
Albumin (g/L)	35.62 ± 5.52	36.76 ± 5.44	34.58 ± 5.38	< 0.001
Globulin (g/L)	26.89 ± 5.31	26.65 ± 5.65	27.10 ± 4.97	0.023
Total bilirubin (µmol/L)	12.23 ± 17.39	13.24 ± 22.53	11.31 ± 10.56	0.004
Direct bilirubin (µmol/L)	6.42 ± 13.74	7.02 ± 17.80	5.87 ± 8.40	0.029
Indirect bilirubin (µmol/L)	5.99 ± 7.48	6.28 ± 6.35	5.71 ± 8.38	0.041
Total bile acid (µmol/L)	7.46 ± 18.67	8.08 ± 21.51	6.88 ± 15.58	0.092
Prealbumin (mg/L)	162.24 ± 79.59	177.45 ± 80.50	148.24 ± 76.12	< 0.001
Alpha-fucosidase (U/L)	23.21 ± 10.46	23.96 ± 10.99	22.51 ± 9.90	< 0.001
Urea (mmol/L)	7.56 ± 8.25	6.94 ± 6.13	8.14 ± 9.76	< 0.001
Creatinine (µmol/L)	133.96 ± 202.80	122.87 ± 178.85	144.17 ± 222.15	0.005
Glomerular filtration rate(ml/min*1.73m ²)	100.00 ± 47.32	104.25 ± 47.97	96.09 ± 46.38	< 0.001
Uric acid (µmol/L)	306.71 ± 132.41	311.28 ± 129.76	302.51 ± 134.72	0.076
Total carbon dioxide (mmol/L)	24.23 ± 11.37	24.48 ± 9.57	24.00 ± 12.81	0.252
Prothrombin time (s)	12.00 ± 2.83	11.90 ± 1.99	12.09 ± 3.43	0.073
International standardization ratio	1.20 ± 6.96	1.02 ± 0.18	1.36 ± 9.64	0.177

Data are n (%) or median (IQ)

Variables	Total (n = 2862)	Control group (n = 1372)	Azvadine group(n = 1490)	<i>p</i>
Fibrinogen (g/l)	4.18 ± 2.62	3.79 ± 1.33	4.54 ± 3.35	< 0.001
Activated partial thromboplastin time (s)	29.74 ± 9.33	29.34 ± 6.43	30.11 ± 11.35	0.025
Thrombin time (s)	16.41 ± 8.77	16.46 ± 8.80	16.36 ± 8.73	0.777
Antithrombin-III (%)	83.92 ± 15.86	85.04 ± 16.81	82.90 ± 14.87	< 0.001
Prothrombin activity (%)	83.75 ± 15.49	84.48 ± 15.86	83.08 ± 15.12	0.016
D-dimer (mg/L)	2.07 ± 5.50	2.06 ± 5.95	2.08 ± 5.04	0.929
Data are n (%) or median (IQ)				

Our main objective was to investigate the association between azvadine treatment and the 28-day mortality rate among hospitalized patients with COVID-19. In the original cohort analysis, no significant impact on the 28-day mortality rate of hospitalized patients with COVID-19 were observed (15.8% vs. 21.8%, $p = 0.065$) (Fig. 2A). However, after PSM and IPTW adjustments, azvadine significantly improved the 28-day mortality rate in hospitalized patients with COVID-19 (20.9% vs. 19.2%, $p = 0.003$ and 21.8% vs. 23.7%, $p = 0.039$, respectively) (Figs. 2B and 2C).

To further investigate the relationship between azvadine treatment and patient mortality rates, this study compared patients in different clinical subtypes, which showed that in patients with mild COVID-19, azvadine treatment did not significantly alter the 28-day mortality rate (3.3% vs. 21.0%, $p = 0.086$) (Fig. 3A). However, in patients with moderate (12.9% vs. 9.5%, $p = 0.043$), severe (37.2% vs. 39.8%, $p = 0.014$), and critical (64.9% vs. 46.4%, $p = 0.008$) conditions, patients receiving azvadine intervention exhibited significantly different 28-day survival rates compared to those receiving standard treatment (Figs. 3B, 3C, and 3D). When azvadine was administered to severe and critical patients, there was a more significant reduction in mortality rates at 7 days (10.1% vs. 1.7% and 34.7% vs. 8.1%, respectively) and 14 days (23.0% vs. 8.4% and 46.5% vs. 22.9%, respectively) (Figs. 3C and 3D). These data show that azvadine can improve the survival rates of patients with COVID-19, particularly for severe and critical patients.

Based on Cox regression analysis, in the original cohort, azvadine treatment reduced 7-day (1.09/1000 people vs. 5.06/1000 people, $p < 0.001$) and 14-day (3.35/1000 people vs. 5.65/1000 people, $p = 0.001$) mortality rates. However, the effect on 28-day mortality (4.38/1000 people vs. 5.65/1000 people, $p = 0.065$) was not significant (Table 2). Post-propensity score matching (PSM), the azvadine group demonstrated significantly improved all-cause mortality rates at 7 days (0.80/1000 people vs. 6.29/1000 people, $p < 0.001$), 14 days (3.42/1000 people vs. 7.26/1000 people, $p < 0.01$), and 28 days (4.33/1000

people vs. 7.29/1000 people, $p = 0.003$). This finding aligns with results following inverse probability of treatment weighting (IPTW) adjustment, where all-cause mortality rates at 7, 14, and 28 days in the azvudine group and control group were 0.93/1000 and 7.07/1000 people ($p < 0.001$), 3.87/1000 and 7.62/1000 people ($p = 0.001$), and 5.15/1000 and 7.69/1000 people ($p = 0.039$), respectively. Subgroup analysis based on COVID-19 clinical grading revealed that in mild patients, azvudine reduced mortality within 7 days (HR: 0.04, 95% CI: 0.00-0.74, $p = 0.030$), but not significantly at 14 days (HR: 1.02, 95% CI: 0.34–3.07, $p = 0.968$) or 28 days (HR: 0.98, 95% CI: 0.34–2.84, $p = 0.966$). In moderate, severe, and critical patients, azvudine significantly reduced mortality rates at 7, 14, and 28 days, with greater effectiveness observed in critical patients.

Table 2
Comparison of mortality rates between Azvudine and conventional treatment groups using COX regression analysis

Variable	rate per 1000 person-days of Control	rate per 1000 person-days of azvudine	P of logrank	HR	adj.HR
Overall					
Before PSM					
7-day	5.06 (3.48 to 6.65)	1.09 (0.45 to 1.73)	< 0.001	0.20(0.10–0.40); P < 0.001	0.11(0.05–0.24); P < 0.001
14-day	5.65 (4.22 to 7.07)	3.35 (2.43 to 4.26)	0.001	0.54(0.37–0.79); P = 0.001	0.34(0.23–0.52); P < 0.001
28-day	5.65 (4.33 to 6.97)	4.38 (3.41 to 5.36)	0.065	0.74(0.53–1.02); P = 0.067	0.43(0.30–0.62); P < 0.001
After PSM					
7-day	6.29 (4.18 to 8.40)	0.80 (0.10 to 1.51)	< 0.001	0.12(0.05–0.32); P < 0.001	-
14-day	7.26 (5.35 to 9.17)	3.42 (2.24 to 4.60)	< 0.001	0.44(0.28–0.68); P < 0.001	-
28-day	7.29 (5.51 to 9.07)	4.33 (3.10 to 5.57)	0.003	0.57(0.39–0.83); P = 0.003	-
After IPTW					
7-day	7.07 (5.80 to 8.34)	0.93 (0.50 to 1.36)	< 0.001	0.13(0.06–0.25); P < 0.001	-
14-day	7.61 (6.50 to 8.72)	3.87 (3.16 to 4.59)	0.001	0.48(0.31–0.75); P = 0.001	-
28-day	7.69 (6.65 to 8.72)	5.15 (4.39 to 5.91)	0.039	0.65(0.42–1.00); P = 0.048	-
clinical typing-I					

Variable	rate per 1000 person-days of Control	rate per 1000 person-days of azvudine	P of logrank	HR	adj.HR
7-day	3.02 (1.15 to 4.89)	0.72 (-0.69 to 2.14)	0.107	0.21(0.03–1.69); P = 0.144	0.04(0.00–0.74); P = 0.030
14-day	2.49 (1.02 to 3.95)	4.43 (1.54 to 7.31)	0.257	1.66(0.69–4.03); P = 0.261	1.02(0.34–3.07); P = 0.968
28-day	2.14 (0.87 to 3.40)	4.72 (1.94 to 7.51)	0.086	2.06(0.89–4.76); P = 0.093	0.98(0.34–2.84); P = 0.966
clinical typing-II					
7-day	1.68 (0.34 to 3.03)	0.15 (-0.14 to 0.44)	0.003	0.08(0.01–0.68); P = 0.020	0.00(0.00–0.00); P < 0.001
14-day	2.87 (1.37 to 4.37)	1.54 (0.76 to 2.31)	0.038	0.47(0.23–0.98); P = 0.043	0.41(0.18–0.96); P = 0.039
28-day	3.23 (1.74 to 4.72)	1.82 (1.02 to 2.62)	0.043	0.52(0.28–0.99); P = 0.047	0.48(0.23–1.00); P = 0.049
clinical typing-III					
7-day	14.59 (5.13 to 24.05)	2.49 (0.05 to 4.93)	0.001	0.17(0.05–0.54); P = 0.003	0.07(0.01–0.89); P = 0.040
14-day	17.36 (9.18 to 25.55)	5.22 (2.49 to 7.95)	< 0.001	0.29(0.14–0.58); P = 0.001	0.28(0.11–0.72); P = 0.008
28-day	16.02 (8.87 to 23.17)	7.58 (4.56 to 10.60)	0.014	0.48(0.26–0.87); P = 0.016	0.54(0.25–1.17); P = 0.120
clinical typing-IV					
7-day	66.99 (33.09 to 100.88)	11.36 (1.46 to 21.27)	< 0.001	0.18(0.06–0.49); P = 0.001	0.05(0.00–0.74); P = 0.029
14-day	51.72 (28.46 to 74.99)	17.08 (7.88 to 26.29)	0.002	0.34(0.17–0.69); P = 0.003	0.37(0.14–0.99); P = 0.048

Variable	rate per 1000 person-days of Control	rate per 1000 person-days of azvudine	P of logrank	HR	adj.HR
28-day	46.51 (27.53 to 65.49)	20.43 (11.98 to 28.88)	0.008	0.45(0.25–0.82); P = 0.009	0.46(0.25–0.85); P = 0.014

DISCUSSION

Azvudine is an RNA-dependent RNA polymerase inhibitor that primarily accumulates in the thymus and peripheral mononuclear cells, promotes immune responses, and inhibits the replication of SARS-CoV-2, thereby reducing lung tissue damage.^[9–10] Azvudine is primarily approved for the treatment of all clinical types of COVID-19.^[11] However, long-term efficacy data for azvudine treatment in patients with COVID-19 are lacking from real-world studies.^[12]

In this retrospective cohort study, 2,862 COVID-19 patients were included, with 1,490 receiving azvudine treatment and 1,372 receiving standard treatment. Initially, no significant difference in the 28-day survival rate was observed between the groups. However, after controlling for confounding factors via PSM and IPTW, and adjusting for variables with $p < 0.05$ in univariate Cox regression analysis, patients receiving azvudine exhibited significantly improved 28-day survival rates compared to those receiving standard treatment ($p = 0.003$ and $p = 0.039$, respectively). Subgroup analyses based on clinical types of COVID-19 patients were conducted to further explore azvudine's effectiveness. Generally, the azvudine group showed lower cumulative mortality rates compared to the control group; however, sudden increases in mortality rates were observed at specific time points (mild, 14 and 28 days) in the azvudine group, suggesting potential variations in treatment effects across different stages or patient populations.

In previous studies, azvudine has been shown to significantly improve patient survival outcomes in the treatment of elderly severe patients with COVID-19,^[13] which is consistent with our findings, although our research involves a broader age range. In a multicenter retrospective randomized cohort study, azvudine demonstrated a significant reduction in overall mortality rates and a decrease in the need for tracheal intubation in moderate to severe patients with COVID-19.^[14] In a cohort study comparing Nirmatrevir-Ritonavir and azvudine, the latter showed comparable efficacy in slowing disease progression and reducing all-cause mortality rates in hospitalized patients with COVID-19.^[10] Although the results of the Phase III clinical trials have not been formally published, several studies have indicated that azvudine can significantly reduce the proportion of disease deterioration and effectively lower the overall mortality rates in real-world applications.^[10, 15] These findings demonstrate the potential and efficacy of azvudine in clinical treatment.

Our study has several limitations. First, we primarily collected data from patients admitted to hospitals in the Ganzhou region of China, but we did not conduct genetic typing of the SARS-CoV-2 virus for all

patients, nor did we include data from other countries or regions, or information on patients of different ethnicities. These factors need to be considered in future studies. Second, despite extensive control for confounding factors in the collected data, we cannot completely rule out the possibility of selection bias. Finally, although our study represents the largest sample size study currently available for evaluating the efficacy of azvudine in treating patients with COVID-19, the sample size is still limited compared to the total number of patients with COVID-19 worldwide. Therefore, the results of this study are only representative of patients in the Ganzhou region, and future research needs to further increase the diversity and quantity of samples to validate our conclusions.

Despite the limitations, our study also demonstrated significant advantages. We observed that azvudine significantly reduces the mortality rate of hospitalized patients with COVID-19 within 28 days, with a pronounced effect in severe and critical cases. These findings indicate that azvudine has enormous potential in the treatment of COVID-19.

CONCLUSIONS

Our study demonstrated that patients with COVID-19 treated with azvudine exhibited a significant reduction in the 28-day mortality rate, with better outcomes observed in severely and critically ill patients, which suggests that azvudine is a favorable treatment option for COVID-19.

Abbreviations

COVID-19	Coronavirus disease 2019
HR	Hazard ratio
CI	Confidence intervals
PSM	Propensity score matching
SMD	Standardized mean difference
IPTW	Inverse probability of treatment weighting

Declarations

Ethics approval and consent to participate

There was no direct patient involvement in the conception, design, or implementation of this study. The requirement for patient consent was waived for this retrospective study, which utilized data from electronic medical records. This study was approved by the Ethics Committee of the First Affiliated Hospital of the Gannan Medical University Hospital (LLSL-2024065).

Consent for publication

Not applicable.

Availability of data and materials

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions Statement

XianfaL and JZ designed the experiments. XiaoL was responsible for clinical assessment of patients. LZ, XZ, LR, and ZZ collected the data. JZ was responsible for data management. JZ and ZZ conducted the statistical analysis. This article was written by ZZ, and reviewed by XianfaL. All the authors have reviewed and approved of the final manuscript.

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Figures

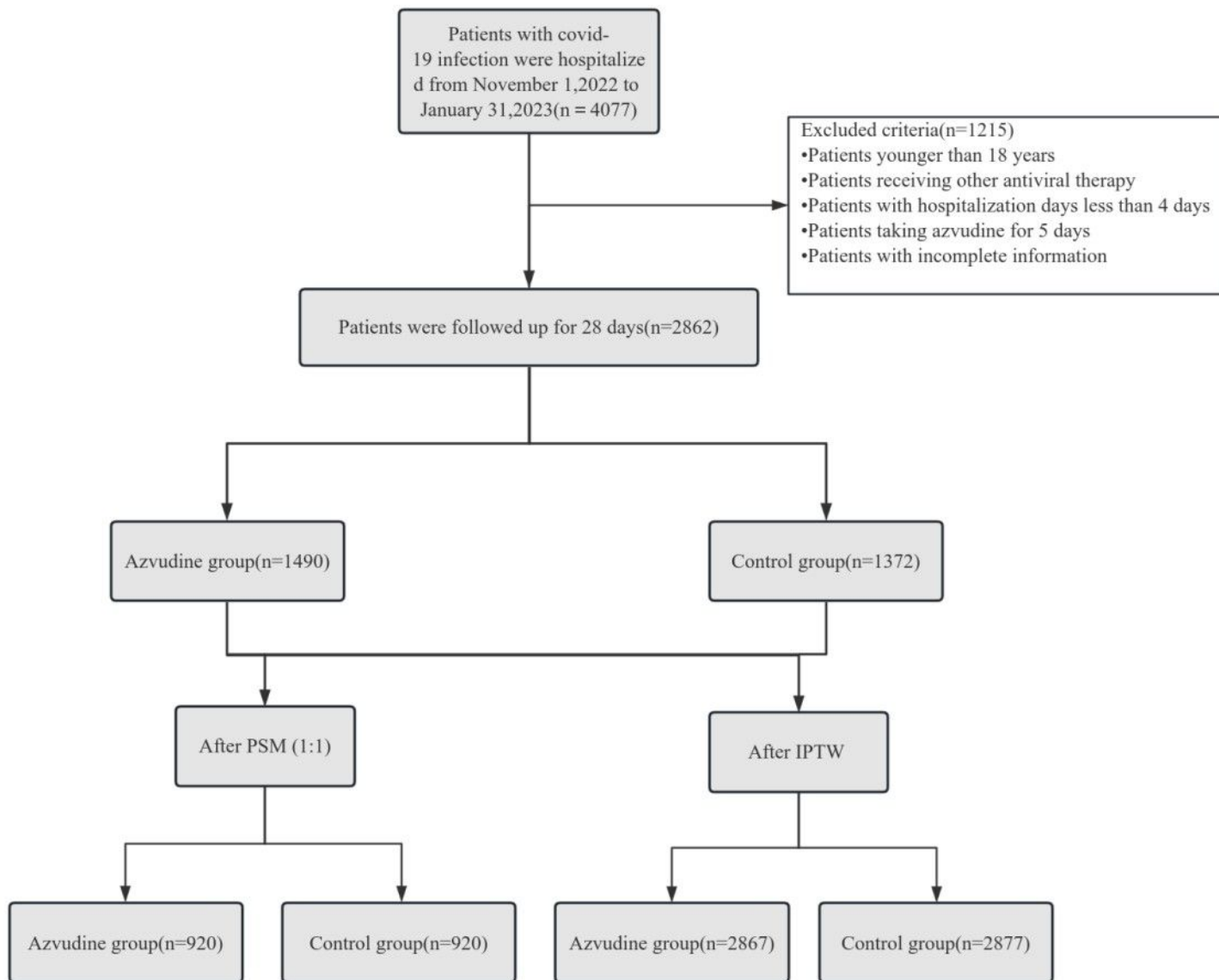


Figure 1

Flowchart of COVID-19 patient selection

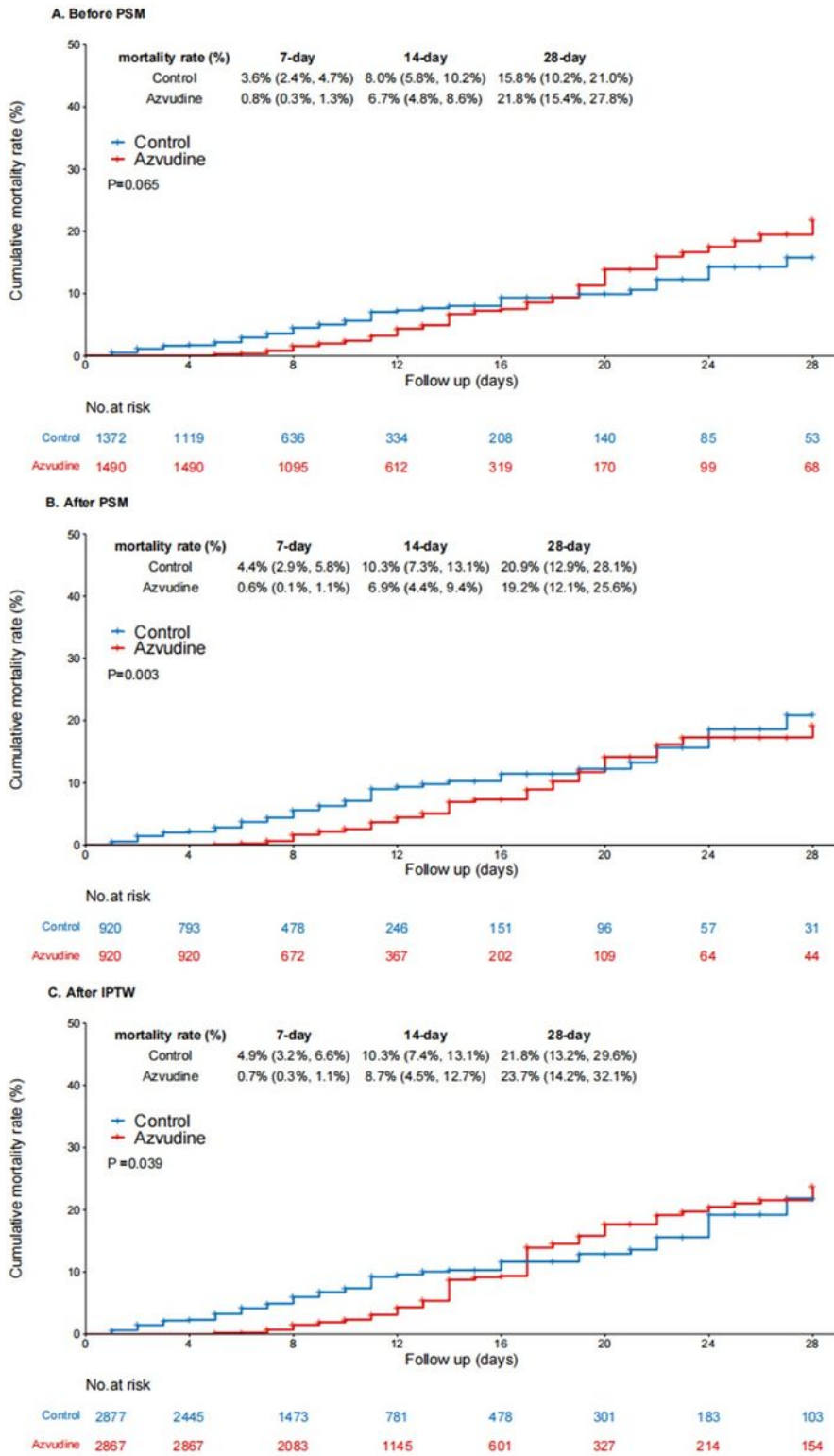


Figure 2

All cause mortality outcomes in Azvudine recipients and control group. A: Original queue; B: After Propensity Score Matching; C: After Inverse Probability of Treatment Weighting

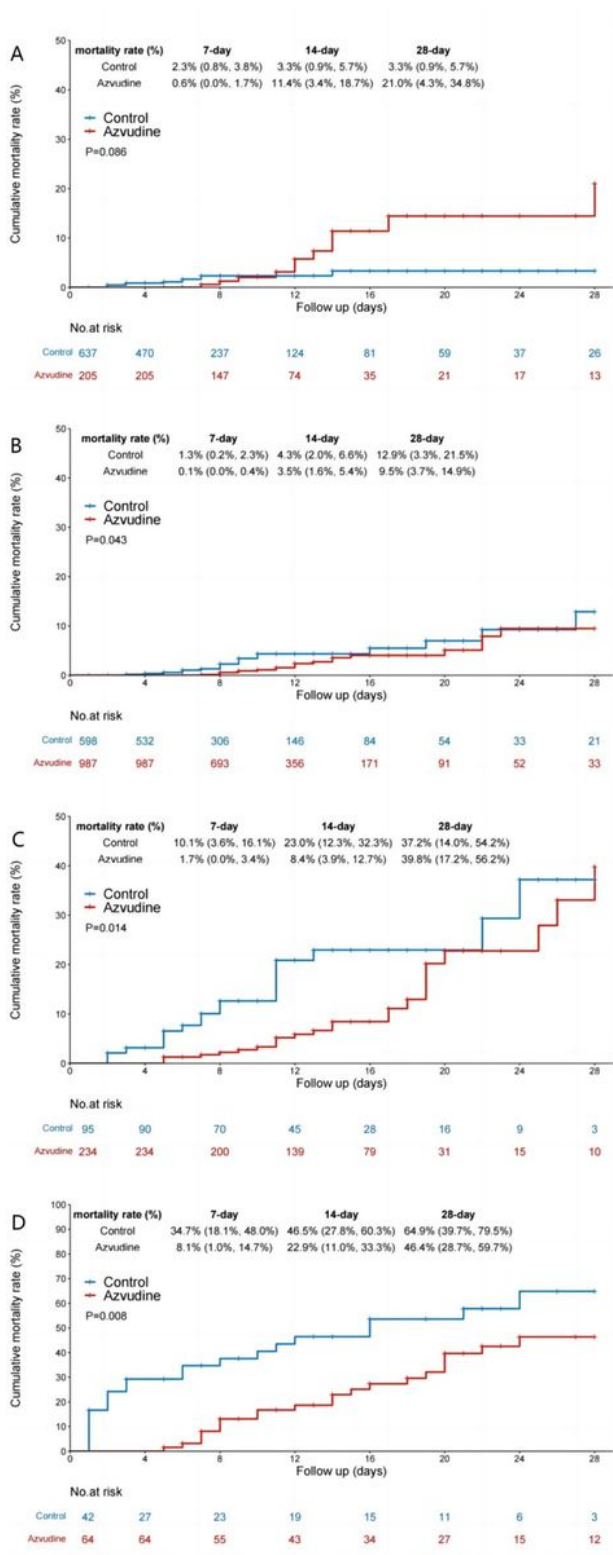


Figure 3

28 day mortality rate of various clinical stages in COVID-19 patients. A: Mild. B: Moderate. C: Severe. D: Critical.

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