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Azvudine efficacy in reducing mortality in COVID-19 patients

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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. This study included mild, moderate, severe, and critical COVID-19 patients to evaluate azvudine's effectiveness across different severity levels.

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 (0.8/1000 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, azvudine treatment intervention significantly reduced the 7-day (2.49/1000 persons vs. 14.59/1000 persons, $P=0.001$ and 11.36/1000 persons vs. 66.99/1000 persons, $P<0.001$), 14-day (5.22/1000 persons vs. 17.36/1000 persons, $P<0.001$ and 17.08/1000 persons vs. 51.72/1000 persons, $P=0.002$), and 28-day (7.58/1000 persons vs. 16.02/1000 persons, $P=0.014$ and 20.43/1000 persons vs. 46.51/1000 persons, $P=0.008$) mortality rates in hospitalized patients with severe and critical COVID-19.

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.

Keywords Azvudine, COVID-19, Real-world study

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 second 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

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drugs, including Nirmatrelvir/ritonavir, molnupiravir, and azvudine, have been authorized for treating patients with COVID-19 [2–5]. Nirmatrelvir/ritonavir and molnupiravir have shown impressive results in clinical trials and real-world populations. They effectively reduce the risk of hospitalization and death among patients [6, 7]. Their mechanisms mainly involve inhibiting viral replication to alleviate disease symptoms. This leads to achieving therapeutic goals [6, 7]. Previous clinical trials have demonstrated that Nirmatrelvir/ritonavir can reduce hospitalization and mortality risks in high-risk, non-hospitalized COVID-19 patients [8]. however, its efficacy in low-risk patients is less apparent [8]. Ritonavir, a potent CYP3A inhibitor within Nirmatrelvir/ritonavir, interacts with many commonly used medications (e.g., statins, antiarrhythmics, immunosuppressants), limiting its use in patients undergoing multiple drug therapies [9]. Nirmatrelvir/ritonavir requires dose adjustments or should be avoided in patients with moderate to severe renal impairment, and it should also be used with caution in those with severe hepatic impairment [9]. Clinical trials have shown that molnupiravir can significantly reduce the risk of hospitalization and mortality in mild to moderate COVID-19 patients [10]. However, due to its mechanism involving mutagenesis, molnupiravir carries potential mutagenic and carcinogenic risks [11], and its safety profile for pregnant women and individuals of reproductive age remains unclear [12]. Azvudine is an orally administered antiviral drug developed independently in China. It is a broad-spectrum RNA virus inhibitor. Initially developed for HIV, it was later repurposed for COVID-19. Azvudine, a nucleoside analogue, specifically inhibits the RNA-dependent RNA polymerase of SARS-CoV-2, thereby blocking viral RNA synthesis [13]. This mechanism, which directly targets the viral replication process, provides a new therapeutic approach for combating COVID-19 [14]. Azvudine has minimal interactions with the CYP450 enzyme system, reducing the risk of drug–drug interactions [13]. Early clinical studies have demonstrated that azvudine has good safety and tolerability in the treatment of COVID-19, with few side effects.[15]In moderate COVID-19 patients, azvudine reduces the time to viral RNA negativity, lowers viral load, and shortens time to clinical improvement. It also maintains a favorable safety and tolerability profile [16]. In severe or critically ill COVID-19 patients, azvudine shortens the time to viral RNA negativity and improves clinical recovery rates. However, its efficacy in ICU patients or those requiring invasive ventilation still needs further investigation [17].

In summary, while Nirmatrelvir/ritonavir and molnupiravir have played important roles in the treatment of COVID-19, limitations related to drug interactions, safety, and efficacy have constrained their broader application. These limitations underscore the need for the development of new antiviral therapies. Azvudine, with its distinct mechanism of action, fewer drug interactions, and favorable safety profile, may offer a new treatment option for COVID-19 patients, addressing unmet medical needs. This study represents the largest single-center retrospective cohort design to date, using propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) to control for confounding factors, thereby enhancing the scientific rigor and reliability of the analysis. In addition, this research encompasses a broad range of hospitalized COVID-19 patients and uniquely demonstrates that Azvudine significantly reduces mortality at 7, 14, and 28 days, particularly among severe and critically ill patients, filling a gap in the current literature regarding the efficacy of this drug in high-risk groups. By conducting multidimensional mortality analyses at various time points, this study not only reveals Azvudine's short-term impact on improving patient prognosis but also provides direct evidence of its effect on survival rates, contrasting with other studies that primarily focus on viral clearance rates. These findings contribute new evidence to the ongoing treatment strategies for COVID-19.

Methods

Study design and participants

This retrospective single-center study was conducted at 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 [18]. The COVID-19 patients included in the study were classified into four clinical subtypes: mild, moderate, severe, and critical [18]. Azvudine treatment was initiated within 24 h of diagnosis, with a dosage of 5 mg administered once daily for up to 14 days. For patients with renal insufficiency, dosage adjustments were made. Institutional Review Board approval was obtained from 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, regardless of gender and (2) 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 receiving antiviral treatments for human immunodeficiency virus, hepatitis B, hepatitis C, nirmatrelvir–ritonavir, molnupiravir, remdesivir, or arbidol; (2) patients with hospital stays < 4 days; (3) patients receiving azvudine for < 5 days; and (4) 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, medication records, nucleic acid diagnosis time, and laboratory tests were gathered. 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 ± 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 compared between groups using the Chi-square test or Fisher's exact test. The Kaplan–Meier survival curve analysis and log-rank test were used to compare differences in mortality rates at different time points between treatment groups. Univariate and multivariate Cox regression analyses were used to estimate 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 for 1:1 PSM to control for confounding factors. The propensity score was calculated using a binary logistic model, with a caliper set at 0.1. Confounding variables included those with $P < 0.1$ in the univariate Cox regression analysis. After PSM, Kaplan–Meier curves and log-rank tests were used to validate the association between treatment groups and mortality, and Cox regression models were used to estimate the HRs and 95% CIs. To further compare differences in mortality rates between treatment groups, we conducted IPTW to control for confounding factors. 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.

Results

Patient cohort and baseline characteristics

From December 1, 2022, to January 31, 2023, we collected data from 4077 patients with COVID-19 in our hospital. After applying the exclusion criteria, a total of 2862 patients were included in this study. Of these, 1,490 received azvudine treatment, while 1372 received 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. Preliminary data indicated differences between the two groups in several variables. Specifically, the azvudine group had a higher proportion of males, older age, and more severe cases compared to the control group. To ensure comparability between the groups, we adjusted for variables with $P < 0.05$ in the univariate Cox regression analysis (S1) and conducted 1:1 propensity score matching (PSM).

After PSM, we identified 920 patients receiving azvudine treatment and 920 patients in the control group for analysis. The baseline characteristics of both groups remained balanced, with a standardized mean difference (SMD) < 0.1 (S2, S4). In addition, after inverse probability of treatment weighting (IPTW) matching, a total of 2867 azvudine-treated patients and 2877 patients receiving standard treatment were included, with an SMD < 0.1 (S3, S4).

Mortality outcomes before and after adjustments

In the original cohort analysis, no significant impact on the 28-day mortality rate was observed in hospitalized patients with COVID-19 (15.8% vs. 21.8%, $P = 0.065$) (Fig. 2A). However, after adjusting for confounding factors using PSM and IPTW, azvudine 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) (Fig. 2B, C).

To further investigate the relationship between azvudine treatment and patient mortality rates, we compared patients in different clinical subtypes. In mild COVID-19 patients, azvudine 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 conditions (64.9% vs. 46.4%, $P = 0.008$), those receiving azvudine intervention exhibited significantly different 28-day survival rates compared to those receiving standard treatment (Fig. 3B–D).

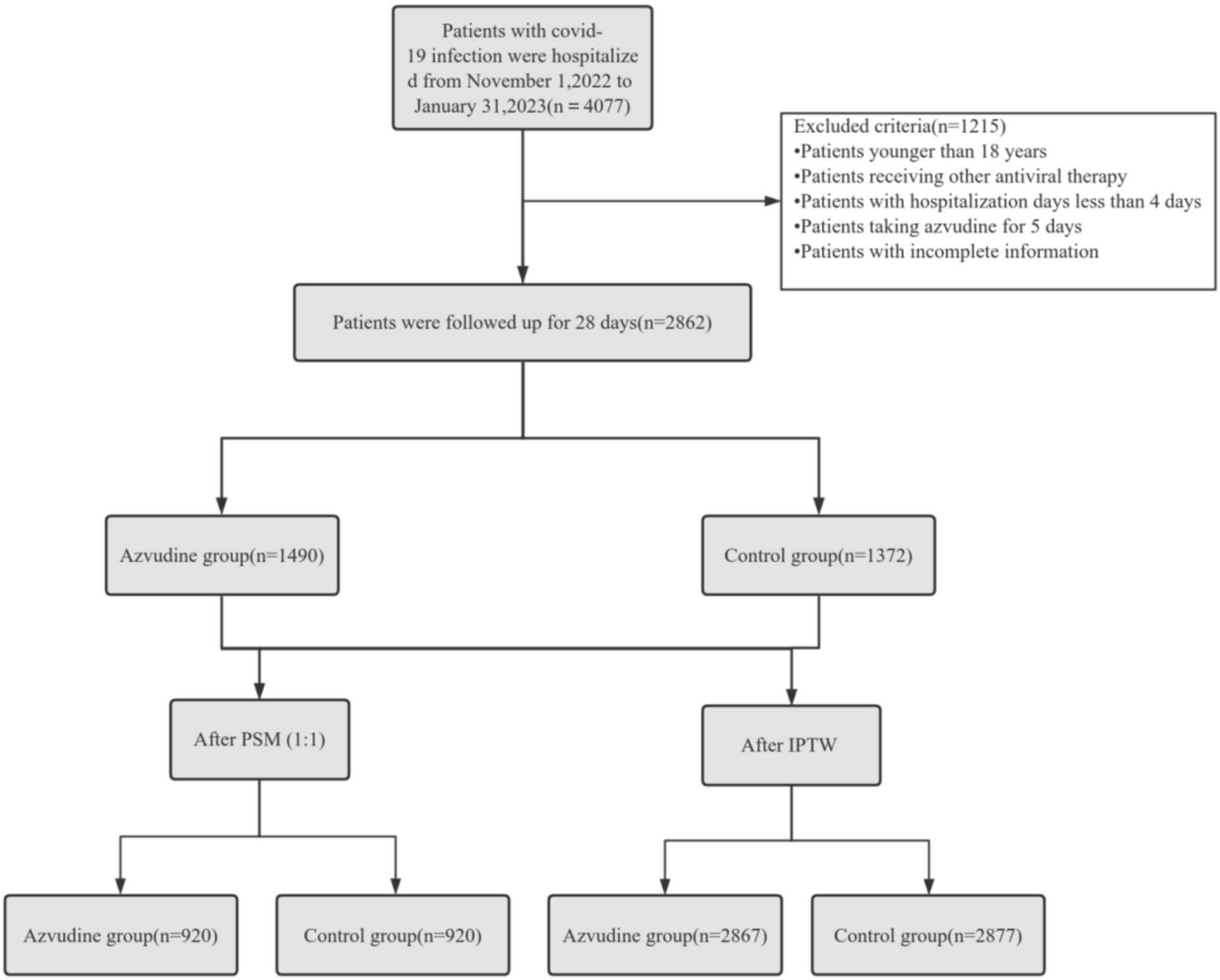

Fig. 1 Flowchart of COVID-19 patient selection

When administered to severe and critical patients, azvudine showed 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) (Fig. 3C, D). These data indicate that azvudine can improve the survival rates of patients with COVID-19, particularly for severe and critical patients.

Cox regression analysis

Based on Cox regression analysis, in the original cohort, azvudine 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, the azvudine 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 IPTW adjustment.

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.

Discussion

In this study, azvudine was shown to reduce the 7-day, 14-day, and 28-day mortality rates in hospitalized COVID-19 patients, with a significant effect observed in

Table 1 Characteristics of the patients with COVID-19

Variables	Total ($n=2862$)	Control group ($n=1372$)	Azvudine group ($n=1490$)	*P*
29-day survival, *n* (%)				
Survival	2715 (94.9)	1302 (94.9)	1413 (94.8)	0.937
All-cause death	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* (%)				
Men	1654 (57.8)	715 (52.1)	939 (63)	< 0.001
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* (%)				
No	2512 (87.8)	1219 (88.8)	1293 (86.8)	0.091
Yes	350 (12.2)	153 (11.2)	197 (13.2)	
Hypertension, *n* (%)				
No	1636 (57.2)	843 (61.4)	793 (53.2)	< 0.001
Yes	1226 (42.8)	529 (38.6)	697 (46.8)	
Diabetes mellitus, *n* (%)				
No	2269 (79.3)	1138 (82.9)	1131 (75.9)	< 0.001
Yes	593 (20.7)	234 (17.1)	359 (24.1)	
Chronic kidney disease, *n* (%)				
No	2538 (88.7)	1232 (89.8)	1306 (87.7)	0.070
Yes	324 (11.3)	140 (10.2)	184 (12.3)	
Chronic obstructive pulmonary disease, *n* (%)				
No	2499 (87.3)	1216 (88.6)	1283 (86.1)	0.043
Yes	363 (12.7)	156 (11.4)	207 (13.9)	
Cancer, *n* (%)				
No	2477 (86.5)	1137 (82.9)	1340 (89.9)	< 0.001
Yes	385 (13.5)	235 (17.1)	150 (10.1)	
Clinical types, *n* (%)				
Mild	842 (29.4)	637 (46.4)	205 (13.8)	< 0.001
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
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

Table 1 (continued)

Variables	Total ($n=2862$)	Control group ($n=1372$)	Azvudine group ($n=1490$)	*P*
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*1.73 m^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
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)

severe and critically ill patients. After adjusting for baseline characteristics using PSM and IPTW, the azvudine group demonstrated more pronounced efficacy. A study by Sun et al. on the efficacy of azvudine in hospitalized COVID-19 patients with comorbidities found that azvudine effectively reduced both disease progression and mortality risk, which aligns with the findings of this study [19]. In addition, while Sun et al.'s research indicated no significant difference in all-cause mortality, while this study showed that after PSM, azvudine significantly reduced mortality at different time points· [19] The mortality rate in the azvudine group was significantly lower than that in the standard treatment group. In another study, Ren et al. demonstrated that azvudine shortened the time to viral RNA negativity in mild and moderate COVID-19 patients [15]. This is consistent with our findings, showing that azvudine effectively inhibits viral replication, facilitating faster recovery. While Ren et al.'s study had a smaller sample size, this study included a larger sample and focused more on mortality as a key clinical endpoint [15].

Currently, head-to-head studies comparing azvudine with other antiviral drugs for COVID-19 are relatively limited. Existing studies suggest that both Nirmatrelvir/ritonavir and azvudine are equally effective in reducing mortality, but Nirmatrelvir/ritonavir shows a more pronounced advantage in shortening the time to nucleic acid negative conversion compared to azvudine [20, 21]. However, Nirmatrelvir/ritonavir did not show a clear advantage in reducing mortality [20, 21]. Conversely, another study suggested that azvudine offers a greater survival benefit compared to Nirmatrelvir/ritonavir in the treatment of COVID-19 patients [22]. The efficacy of molnupiravir in severe cases is relatively weak, being primarily suited for mild to moderate cases [23]. Azvudine is not only effective in mild cases but also demonstrates particularly strong efficacy in severe cases [23]. This conclusion is in line with our findings.

Azvudine, as a nucleoside analogue, raises concerns about potential hepatotoxicity, a common issue associated with this class of drugs. Previous studies have demonstrated good tolerability with minimal side effects in HIV patients [24]. A retrospective study found that the safety and efficacy of azvudine in treating COVID-19 patients were comparable to those of Nirmatrelvir–Ritonavir [20]. Another clinical trial showed that azvudine exhibited good safety in the treatment of COVID-19 patients, with common side effects including mild gastrointestinal discomfort, which was generally acceptable [25]. These findings suggest that azvudine is a safe option for treating COVID-19 patients. In terms of cost-effectiveness, azvudine has a relatively lower production cost and market price compared to Nirmatrelvir/ritonavir and molnupiravir. This makes it a more feasible treatment option, particularly in the context of a prolonged global pandemic, especially for developing countries.

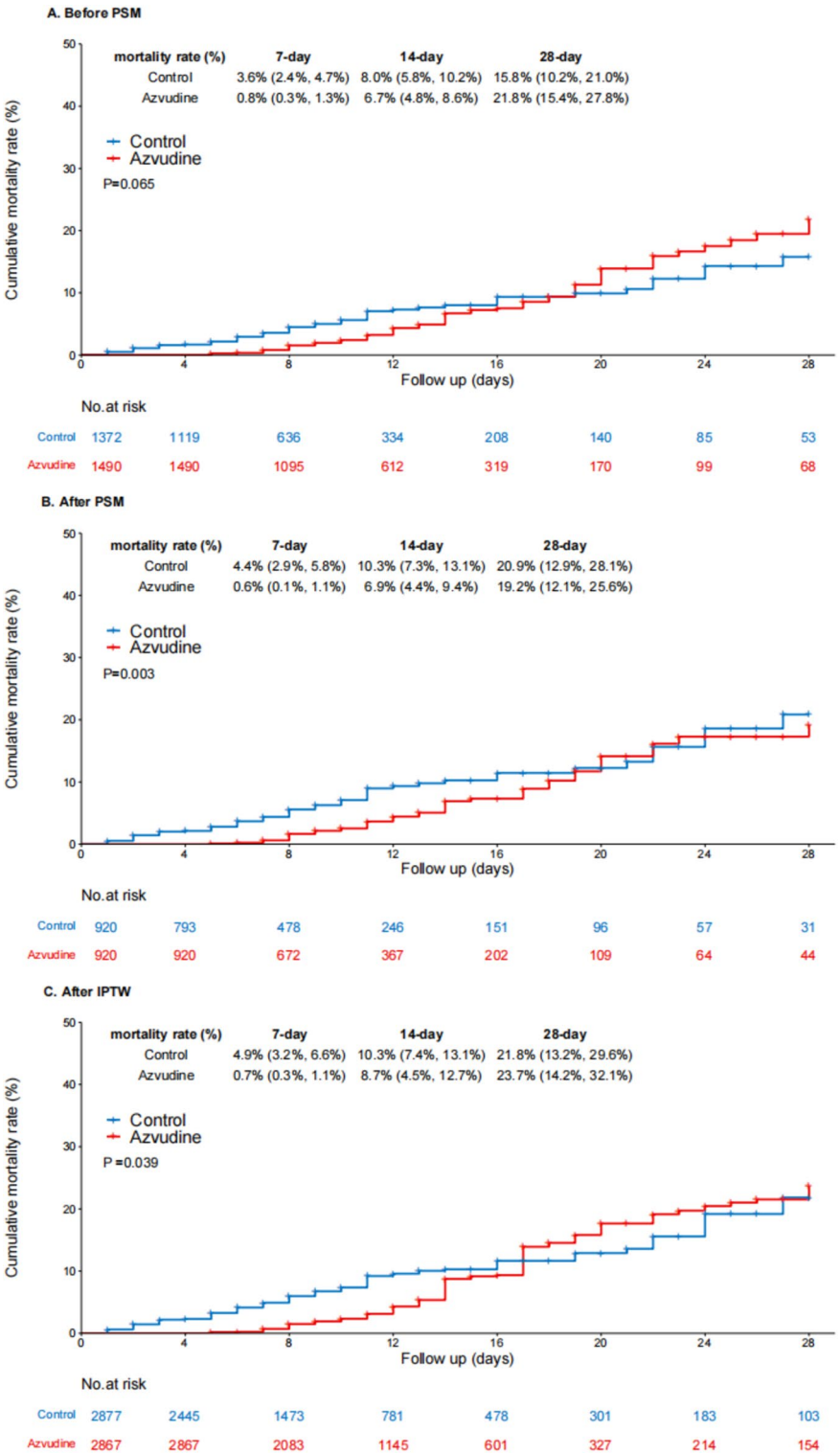

Fig. 2 All cause mortality outcomes in azvudine recipients and control group. **A** Original queue; **B** after propensity score matching; **C** after inverse probability of treatment weighting

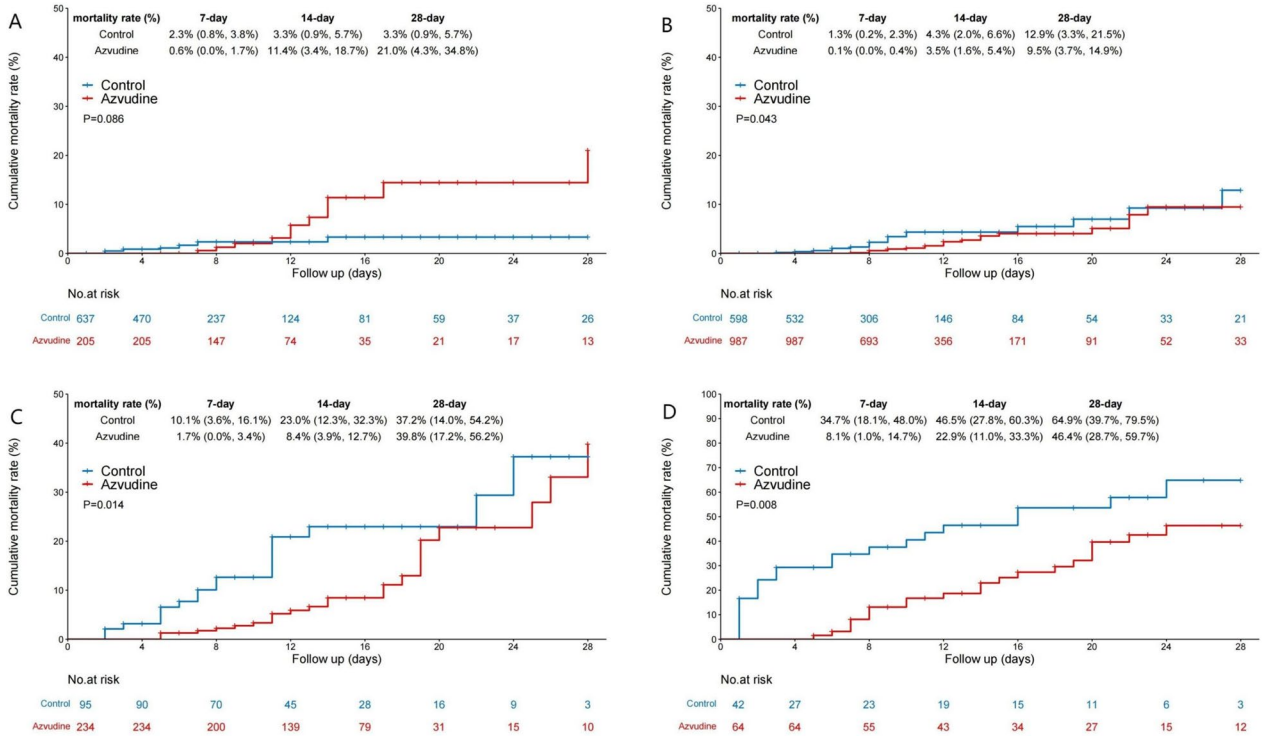

Fig. 3 28-day mortality rate of various clinical types in COVID-19 patients. **A** Mild. **B** Moderate. **C** Severe. **D** Critical

There are some limitations to this study. First, as a single-center retrospective study, the generalizability of the findings may be limited. Since the study involved patients from only one medical center, the results may not be representative of patient populations from other regions or healthcare systems. The possibility of selection bias cannot be entirely ruled out. For example, we observed a significant increase in mortality 12 days after treatment in mild COVID-19 cases, which may be related to baseline characteristics of the patients. Although we used PSM and IPTW to reduce the impact of confounding factors, there may still be unquantifiable risk factors, particularly in mild cases. The follow-up period in this study was 28 days. While this is sufficient to assess short-term mortality, the impact on long-term complications and survival remains unclear. In addition, the continuous emergence of viral variants, particularly the Omicron variant, poses new challenges. Future research should include longer follow-up periods to evaluate azvudine's efficacy against different variants and to assess its long-term effects and safety.

Conclusions

This study demonstrated the efficacy of azvudine in the treatment of COVID-19 patients, significantly reducing the 7-day, 14-day, and 28-day mortality rates in hospitalized patients, with particularly notable effects in severe and critically ill cases. azvudine has the potential to become a key drug in the global fight against the COVID-19 pandemic.

Table 2 Comparison of mortality rates per 1000 people 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 log rank	HR	adj.HR
Overall					
Before PSM					
7 days	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 days	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 days	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 days	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 days	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 days	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 days	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 days	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 days	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 type-mild					
7 days	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 days	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 days	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 type-moderate					
7 days	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 days	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 days	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 type-severe					
7 days	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 days	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 days	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 type-critical					
7 days	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 days	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); $P = 0.048$
28 days	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); $P = 0.014$

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

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-024-02220-9.

Additional file 1

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Author contributions
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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Availability of data and materials
No datasets were generated or analysed during the current study.

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.

Competing interests
The authors declare no competing interests.

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