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Efficacy of Azvudine Therapy in Patients with Severe and Non-Severe COVID-19: A Propensity Score-Matched Analysis

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Objective: Azvudine is used to treat patients with the coronavirus disease 2019 (COVID-19). This study evaluated the clinical efficacy of azvudine in hospitalized patients with different severities of COVID-19 because few studies have described this in patients with severe and non-severe COVID-19.

Methods: This retrospective study included hospitalized patients with COVID-19 in Guizhou Provincial People's Hospital between December 2022 and January 2023. Azvudine-treated patients and controls were matched for sex, age, and disease severity at admission. Laboratory results and outcomes, including all-cause mortality, invasive mechanical ventilation, intensive care unit admission, and hospital stay length, were evaluated. Stratified analysis was used to explore the difference in the efficacy of azvudine in severe and non-severe COVID-19 patients.

Results: No significant differences in all-cause mortality were observed between the 303 azvudine recipients and 303 matched controls. However, azvudine-treated patients had shorter hospital stays (8.34±4.79 vs 9.17±6.25 days, P=0.046) and higher lymphocyte improvement rates (21.5% vs 13.9%, P=0.019), with a more pronounced effect in patients with non-severe COVID-19 (length of hospital stay, 8.07±4.35 vs 10.00±6.29 days, P=0.001; lymphocyte improvement rate, 23.8% vs 12.8%, P=0.015).

Conclusion: Azvudine treatment shortens hospital stay length and increases the rate of lymphocyte count improvement in patients with non-severe COVID-19, suggesting that azvudine may be a treatment option for these patients.

Keywords: azvudine, COVID-19, severity, effectiveness, clinical outcome, hospital stay length

Introduction

The coronavirus disease 2019 (COVID-19) pandemic continues to threaten global public health and generate a considerable economic burden.[1,2] At the end of 2022, the number of COVID-19 patients surged in China due to changes in the COVID-19 prevention measures and control strategy.[3] Omicron, currently the predominant severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant, has demonstrated higher transmissibility and greater immune escape than previous variants.[4,5] As of August 2024, over 776 million COVID-19 cases and 7 million deaths have been reported globally, according to the World Health Organization. In recent years, efforts have been made to explore antiviral drugs to treat SARS-CoV-2 infection to reduce the death rate of COVID-19 patients.[6] In China, several antiviral drugs have been approved as treatments for COVID-19, including nirmatrelvir/ritonavir, lopinavir/ritonavir, azvudine, molnupiravir, and remdesivir.[7–9] Azvudine was the first domestically developed antiviral drug to treat COVID-19 in China.[10]

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Azvudine is a broad-spectrum, small nucleoside analog inhibitor originally developed for the treatment of human immunodeficiency virus (HIV) infection.[11] Previous studies have demonstrated the long-term efficacy of azvudine in the treatment of acquired immune deficiency syndrome by inhibiting HIV-1 reverse transcription and replication.[12,13] Recently, Azvudine has also been found to reduce the replication of SARS-CoV-2, emerging as a potential treatment for COVID-19.[14] As a prodrug, azvudine can be converted intracellularly to azvudine triphosphate, which can inhibit viral RNA-dependent RNA polymerases and ultimately stop SARS-CoV-2 replication.[15]

Based on the available evidence for azvudine used in COVID-19 treatment, compared to controls, azvudine could reduce the viral load and shorten the time to negative SARS-CoV-2 nucleic acid test results.[16,17] Additionally, azvudine treatment improved lung function in patients with COVID-19 in a randomized controlled trial.[18] A recently published systematic review of 17 studies showed that azvudine reduced the risk of mortality in patients with COVID-19 compared to controls but had no benefits in intensive care unit admission.[19] A Phase III randomized controlled trial revealed that patients receiving azvudine had a shorter hospital stay than controls.[20] Furthermore, a real-world study by Yang et al suggested that azvudine treatment reduced the rate of disease progression and COVID-19-related hospitalization.[21] However, few studies have described the efficacy of azvudine treatment in patients with severe and non-severe COVID-19.

In this retrospective study, we evaluated the clinical efficacy of azvudine in hospitalized patients with COVID-19, including all-cause mortality, the rate of intensive care unit admission, invasive mechanical ventilation, length of hospital stay, and lymphocyte improvement rate. Stratified by COVID-19 severity, this study assessed the efficacy of azvudine in patients with severe and non-severe COVID-19. Our findings provide valuable clinical evidence to support physicians in using azvudine therapy in patients with different COVID-19 severities.

Material and Methods

Study Design and Participants

We conducted a retrospective study of hospitalized patients with a positive reverse-transcription polymerase chain reaction for SARS-CoV-2 nucleic acid at Guizhou Provincial People's Hospital. The enrollment period spanned from December 10, 2022 to January 10, 2023. All participants were administered azvudine plus standard treatment or standard treatment alone. The treatment protocol was based on the Chinese Diagnosis and Treatment Plan for Novel Coronavirus Pneumonia (Trial Version, 10).[22] Patients were excluded if they met any of the following criteria: (1) age < 18 years; (2) received antiviral agents other than azvudine; and (3) died or were intubated or discharged within 24 hours of admission. This study was approved by the Ethics Committee of Guizhou Provincial People's Hospital (No. [2022] 113). Due to the retrospective design and use of anonymized data, the requirement for informed consent was waived.

The severity of COVID-19 was defined according to the Chinese Diagnosis and Treatment Plan for Novel Coronavirus Pneumonia (Trial Version, 10). The severe group included severe and critical COVID-19 cases, whereas the non-severe group included mild and common cases.

Data Collection

Electronic medical records and laboratory results of hospitalized patients with COVID-19 were retrieved from the hospital information system. The data included demographic information (age and sex), comorbidities, medication history, vital signs, diagnoses, prescriptions, and outcome records. We also reviewed laboratory results at admission and after treatment. The improvement rate of the laboratory indicators was defined as the proportion of patients with abnormal levels at admission that returned to normal levels after treatment.

Treatment Exposure

Treatment decisions for patients with COVID-19 were made by physicians based on clinical features and guidelines. Patients with COVID-19 who received oral azvudine during hospitalization were defined as those exposed to treatment. Azvudine was administered orally at a dose of 5 mg once daily for less than 14 days. Controls were patients with COVID-19 who had received neither azvudine nor other antiviral drugs during hospitalization. The patients were also provided other standard treatments, such as prone ventilation, anticoagulants, glucocorticoids, nutritional support, and oxygen therapy, as appropriate.

Outcomes

Outcomes included all-cause mortality, invasive mechanical ventilation, intensive care unit admission, and length of hospital stay. We reviewed the outcomes from the admission date, outcome events, and discharge or death date. We compared the outcomes between the azvudine and control groups among all included patients with COVID-19, patients with severe COVID-19, and patients with non-severe COVID-19.

Statistical Analysis

Multiple imputations were used to handle missing data. Medians and interquartile ranges were calculated for continuous variables and compared using a *t*-test or Wilcoxon rank-sum test. Categorical variables were presented as percentages, and the chi-square test was used for comparison. To help account for the non-randomized treatment administration of azvudine, we used propensity score matching (PSM) to eliminate imbalanced covariates between the two groups and reduce the confounding effects. In the PSM analysis, the nearest-neighbor method was applied to create a matched control sample. The imbalanced covariates mainly included sex, age, and severity of COVID-19 at admission.

Univariate and multivariate Cox proportional hazard regression models were used to estimate the association between azvudine use and all-cause mortality. In addition, inverse probability weighting (IPW) was used to perform sensitivity analyses. Individual propensities for receiving azvudine treatment were estimated using a multivariable logistic regression model that included the same covariates as those used in the Cox regression model to calculate the stabilized IPW weight. Kaplan–Meier curves and Cox models using IPW weights are reported. The nonparametric bootstrap method was used to obtain 95% pointwise confidence intervals for the IPW Kaplan–Meier curves.

Stratified analysis was used to explore the differences in the efficacy of azvudine in patients with severe and non-severe COVID-19. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using R software, version 4.2.3 (R Project for Statistical Computing).

Results

Patient Characteristics

We consecutively collected data of 1126 hospitalized patients with COVID-19 between December 10, 2022 and January 10, 2023. A total of 778 patients were eligible for inclusion. Ultimately, 303 patients were included in the azvudine group (median treatment duration, 5 days) and 475 in the control group (Figure 1). The demographic and clinical characteristics of patients before and after 1:1 PSM are shown in Table 1. In the unmatched sample, patients treated with azvudine were older (68.8±16.3 vs 60.8±21.1 years, P<0.001) and included more males (59.1% vs 49.7%, P=0.013) compared with those in the control group. The proportion of severe COVID-19 cases at admission appeared to be higher in the azvudine group compared to the control group (45.5% vs 34.7%, P=0.003). After PSM, we included 303 azvudine recipients and 303 matched patients who did not receive azvudine. The baseline characteristics of the two groups were balanced; no significant differences were observed between the two groups in terms of sex, age, or COVID-19 severity at admission.

Clinical Outcomes and Laboratory Findings

In the matched cohort, the all-cause mortality rate was 16.2% in the azvudine group and 12.2% in the control group, showing no significant difference between the two groups (P=0.200). Likewise, in the multivariate, IPW, and PSM analyses, azvudine was not superior to the control treatment with respect to all-cause mortality (Table S1 and Figure 2). There were no statistically significant differences between the two groups in the rates of intensive care unit admission (P = 0.890) or invasive mechanical ventilation initiation (P=0.216). However, patients treated with azvudine had shorter hospital stays than those in the control group (8.34±4.79 vs 9.17±6.25 days, P=0.046) (Table 2).

Among the laboratory outcomes, the improvement rates of leukocyte and neutrophil counts were similar between the two groups (Figure 3). However, a significant beneficial effect of azvudine in terms of the lymphocyte improvement rate was detected (21.5% vs 13.9%, P=0.019). There were no significant differences in the levels of alanine aminotransferase, total bilirubin, direct bilirubin, indirect bilirubin, serum creatinine, or estimated glomerular filtration rate between the two groups after treatment (Figure S1).

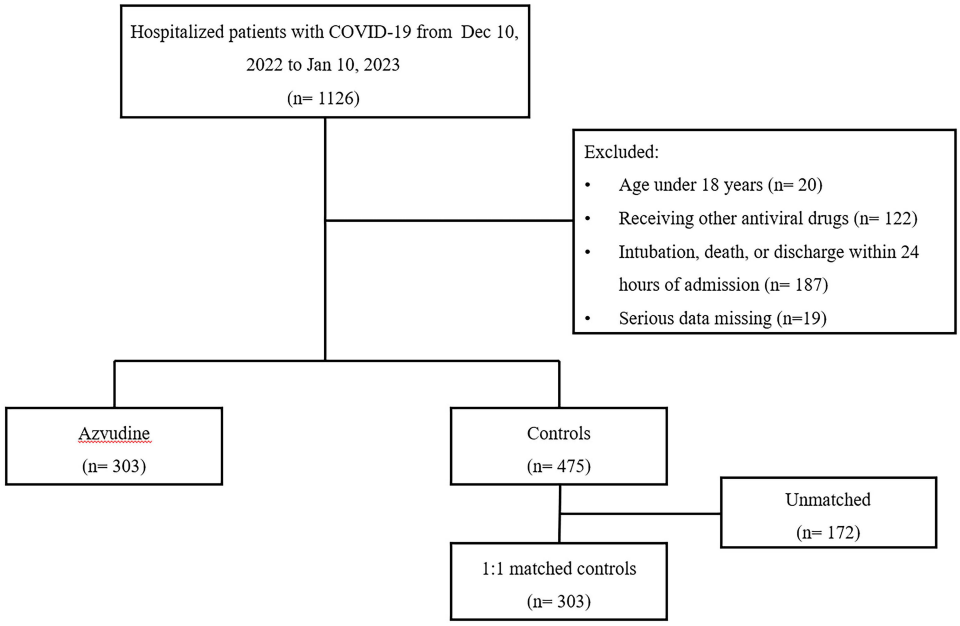

Figure 1 Flow chart of patients screening.

Subgroup Analysis of Patients with Non-Severe COVID-19

Of the 778 enrolled patients, 475 were considered to have non-severe COVID-19, and 303 were considered to have severe COVID-19 at admission. Among the non-severe COVID-19 cohort, 165 were treated with azvudine, and 310 were not. Table S2 shows the baseline characteristics of patients with non-severe COVID-19 before and after PSM. After matching, 164 azvudine recipients and 164 patients who were not treated with azvudine were included. The baseline characteristics were comparable between the two groups.

Table 1 Baseline Characteristics of Patients Receiving or Not Receiving Azvudine Before and After Propensity Score Matching

Baseline Characteristics	Before Matching Patients			After Propensity-Score Matching Patients		
	Azvudine (n=303)	Control (n=475)	P Value	Azvudine (n=303)	Control (n=303)	P Value
Age, (years)	68.8±16.3	60.8±21.1	<0.001	68.8±16.3	68.6±16.1	0.860
Sex, n (%)			0.013			0.681
Male	179 (59.1%)	236 (49.7%)		179 (59.1%)	173 (57.1%)	
Female	124 (40.9%)	239 (50.3%)		124 (40.9%)	130 (42.9%)	
Severity at admission, n (%)			0.003			0.218
Non-severe	165 (54.5%)	310 (65.3%)		165 (54.5%)	181 (59.7%)	
Severe	138 (45.5%)	165 (34.7%)		138 (45.5%)	122 (40.3%)	
Smoking, n (%)	62 (20.5%)	97 (20.4%)	1.000	62 (20.5%)	68 (22.4%)	0.621
BMI	23.6±3.79	23.4±4.08	0.420	23.6±3.79	23.1±3.60	0.135
Comorbidities, n (%)						
Diabetes	67 (22.1%)	107 (22.5%)	0.963	67 (22.1%)	75 (24.8%)	0.502
Hypertension	149 (49.2%)	174 (36.6%)	<0.001	149 (49.2%)	134 (44.2%)	0.254
Coronary heart disease	43 (14.2%)	76 (16.0%)	0.561	43 (14.2%)	58 (19.1%)	0.127
COPD	23 (7.6%)	35 (7.4%)	1.000	23 (7.6%)	24 (7.9%)	1.000
Cancer	34 (11.2%)	87 (18.3%)	0.010	34 (11.2%)	53 (17.5%)	0.037
Renal insufficiency	87 (18.3%)	63 (13.3%)	0.961	39 (12.9%)	46 (15.2%)	0.483

(*Continued*)

Table 1 (Continued).

Baseline Characteristics	Before Matching Patients			After Propensity-Score Matching Patients		
	Azvudine (n=303)	Control (n=475)	P Value	Azvudine (n=303)	Control (n=303)	P Value
Concomitant medications, n (%)						
Systemic steroid	242 (79.9%)	187 (39.4%)	<0.001	242 (79.9%)	130 (42.9%)	<0.001
Antibiotics	217 (71.6%)	287 (60.4%)	0.002	217 (71.6%)	179 (59.1%)	0.002
ACE inhibitor or ARB	46 (15.2%)	55 (11.6%)	0.178	46 (15.2%)	42 (13.9%)	0.729
Anticoagulant	174 (57.4%)	147 (30.9%)	<0.001	174 (57.4%)	100 (33.0%)	<0.001
Baricitinib	4 (1.3%)	3 (0.6%)	0.547	4 (1.3%)	3 (1.0%)	1.000
Initial vital signs						
Systolic blood pressure, (mmHg)	126±18.3	123±17.5	0.033	126±18.3	126±17.6	0.912
Diastolic blood pressure, (mmHg)	76.4±12.1	74.4±11.5	0.018	76.4±12.1	75.7±11.5	0.448
Heart rate, (beats/min)	83.8±13.2	85.7±14.6	0.061	83.8±13.2	84.9±15.4	0.331
Respiratory rate, (breaths/min)	20.5±2.35	20.8±9.29	0.461	20.5±2.35	21.2±11.5	0.305
Oxygen saturation, (%)	93.3±6.12	94.8±3.23	<0.001	93.3±6.12	94.4±3.61	0.008
Initial laboratory tests						
Leukocytes, ($\times10^9$/L)	5.62 [4.33–7.76]	6.24 [4.50–8.73]	0.048	5.62 [4.33–7.76]	6.31 [4.50–8.68]	0.047
Neutrophil count, ($\times10^9$/L)	5.04±3.58	5.36±3.76	0.241	5.04±3.58	5.52±3.96	0.121
Lymphocyte count, ($\times10^9$/L)	0.94 [0.62–1.41]	1.03 [0.68–1.54]	0.051	0.94 [0.62–1.41]	0.97 [0.64–1.43]	0.553
C-reactive protein, (mg/L)	35.6 [9.04–82.7]	13.9 [4.22–54.3]	<0.001	35.6 [9.04–82.7]	16.8 [4.27–64.6]	<0.001
D-Dimer, (mg/L)	0.95 [0.63–1.69]	0.99 [0.59–2.16]	0.634	0.95 [0.63–1.69]	0.97 [0.61–2.25]	0.651
ALT, (IU/L)	23.0 [15.0–37.0]	19.0 [13.0–34.0]	0.003	23.0 [15.0–37.0]	20.0 [13.0–34.0]	0.064
Serum creatinine, (umol/L)	77.0 [65.0–94.0]	77.0 [65.0–94.0]	0.092	77.0 [65.0–94.0]	78.0 [64.5–103.0]	0.619
eGFR, (mL/min)	75.0±26.7	80.9±33.2	0.007	75.0±26.7	73.8±29.8	0.603

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ACE, Angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ALT, alanine aminotransferase; e-GFR, estimated glomerular filtration rate.

Among the matched patients with non-severe COVID-19, the all-cause mortality rate was 4.3% in the azvudine group and 3.0% in the control group, with no significant difference between the two groups (Table 2). Azvudine treatment in patients with non-severe COVID-19 was not significantly associated with the rate of invasive mechanical ventilation (1.8% vs 0.6%, P=0.623) or intensive care unit admission (3.7% vs 0.6%, P=0.126). Compared with the control group,

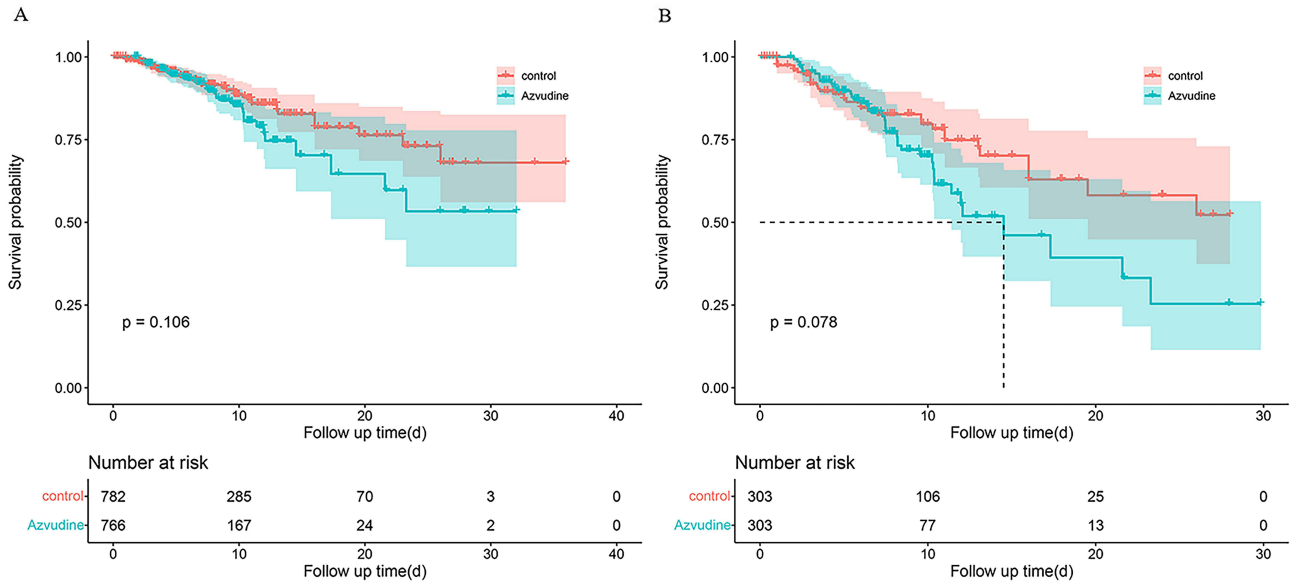

Figure 2 Kaplan-Meier charts showing all-cause mortality using probability weighting analysis in all patients (**A**) and in patients with severe COVID-19 (**B**).

Table 2 Clinical Outcomes Among Azvudine Recipients versus Matched Controls

Outcome	All			Non-Severe			Severe		
	Azvudine (n=303)	Control (n=303)	P Value	Azvudine (n=164)	Control (n=164)	P Value	Azvudine (n=137)	Control (n=137)	P Value
All-cause death, n (%)	49 (16.2%)	37(12.2%)	0.200	7(4.3%)	5(3.0%)	0.770	41 (29.9%)	31(22.6%)	0.217
Invasive mechanical ventilation, n (%)	21 (6.9%)	13(4.5%)	0.216	3(1.8%)	1(0.6%)	0.623	18 (13.1%)	12(8.8%)	0.333
Intensive care unit admission, n (%)	30 (9.9%)	28 (9.2%)	0.890	6 (3.7%)	1 (0.6%)	0.126	24 (17.5%)	27 (19.7%)	0.756
Length of hospital stay, (days)	8.34±4.79	9.17±6.25	0.046	8.07±4.35	10.00 ±6.29	0.001	8.67±5.27	8.40±6.27	0.700

azvudine was associated with a significantly shorter hospital stay (8.07±4.35 vs 10.00±6.29 days, P=0.001). Moreover, the lymphocyte improvement rate was significantly higher in patients with non-severe COVID-19 receiving azvudine than in those receiving the control treatment (23.8% vs 12.8%, P=0.015) (Figure 3). There were no significant differences in the improvement rate of leukocyte or neutrophil counts.

Subgroup Analysis of Patients with Severe COVID-19

Of the 303 patients with severe COVID-19, 138 were treated with azvudine, and 165 were in the control group. The baseline characteristics of the patients with severe COVID-19 before and after PSM are presented in Table S3. After PSM, the azvudine and control groups comprised 137 participants each. Sex, age, and the severity of COVID-19 at admission were balanced between the matched groups.

In terms of clinical outcomes, no significant differences were observed in the all-cause mortality, intubation rate, or ICU admission between the azvudine and control groups (Table 2). After multivariate, IPW, and PSM analyses, there was no significant difference in all-cause mortality between the two groups (Table S4 and Figure 2). Compared to the control group, the groups of severe COVID-19 patients treated with azvudine experienced no significant advantage in terms of length of hospital stay (8.67±5.27 vs 8.40±6.27 days, P=0.700). There were no significant differences in the improvement rates of lymphocyte, leukocyte, or neutrophil counts (Figure 3).

Discussion

This was a retrospective study on the efficacy of azvudine in patients with severe and non-severe COVID-19. After PSM, the study included 303 azvudine recipients and 303 controls. We found that azvudine administration was associated with a shorter hospital stay and a higher improvement rate of lymphocyte count without impairing liver and kidney function, particularly in patients with non-severe COVID-19.

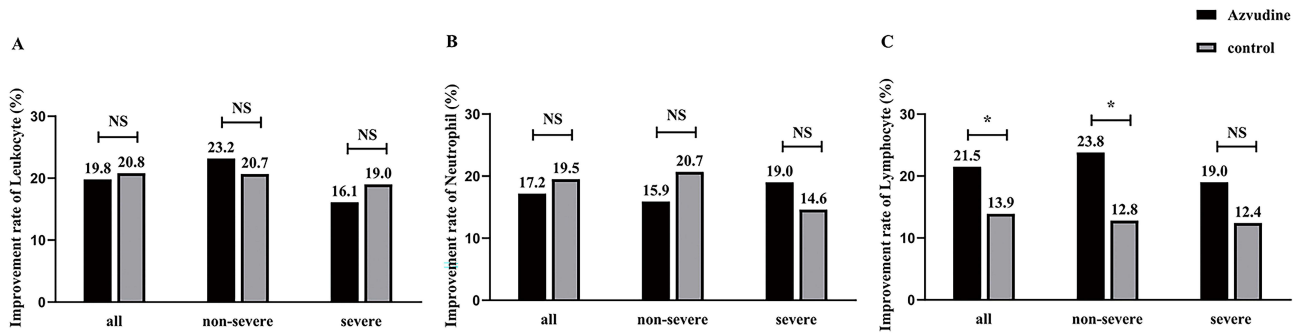

Figure 3 Comparison of the improvement rate of leukocytes (**A**), neutrophils (**B**), and lymphocytes (**C**) in the azvudine treatment group and matched control group. *P < 0.05; NS, not significant.

In this cohort, for patients with severe and non-severe COVID-19, the azvudine group had a similar all-cause mortality rate to that of the control group. Consistent with our findings, Sun et al[23] found no significant difference in mortality between patients with COVID-19 receiving azvudine and those who did not. However, several real-world studies have shown a significant beneficial effect of azvudine on mortality.[24–26] Shao et al also observed that azvudine treatment may improve 60-day mortality.[27] Additionally, a meta-analysis demonstrated that compared to control treatments, azvudine reduced the risk of mortality in patients with COVID-19 and had benefits in both mild-to-moderate and severe COVID-19 patients.[19] This result may be because patients in the azvudine group had lower oxygen saturation and higher C-reactive protein levels on admission and were more severely ill than patients in the control group. The short observation period in our study, which was insufficient to distinguish differences in mortality, may also offer an explanation.

In this study, azvudine-treated patients, particularly those with non-severe COVID-19, had significantly shorter length of hospital stay than patients in the control group. These findings are consistent with recent reports that azvudine treatment is associated with a shorter hospital stay (7.00±1.41 vs 13.00±4.30 days, P=0.02).[18] A systematic review reported similar findings, showing that azvudine treatment for patients with COVID-19 resulted in a significant decrease in the length of hospital stay.[17] A possible explanation for these findings may be the rapid nucleic acid-negative conversion and improvement of symptoms in patients with COVID-19 receiving azvudine, making it easier for the patients to meet the discharge criteria. Several studies have confirmed that the administration of azvudine can decrease viral load, expedite nucleic acid-negative conversion, and accelerate the improvement of symptoms.[16,21,28] Recently, the active ingredients of azvudine were found to accumulate mainly in the thymus, inhibiting SARS-CoV-2 replication to treat COVID-19.[29,30]

Lymphopenia is an important laboratory abnormality caused by SARS-CoV-2 infection.[31] Several factors contribute to lymphopenia in patients with COVID-19. Research has revealed that angiotensin-converting enzyme 2 is expressed on the surface of lymphocytes, and SARS-CoV-2 can cause lymphopenia by directly infecting these cells.[32] In addition, the increased levels of many cytokines, including granulocyte colony-stimulating factor, interleukin-6, and interleukin-7, could promote lymphocyte apoptosis.[33,34] Lymphopenia in patients with COVID-19 has been associated with poor outcomes, including acute respiratory distress syndrome, ICU admission, and mortality.[24,35,36] Luo et al[37] found that peripheral blood lymphocyte count was negatively correlated with SARS-CoV-2 clearance. Our study showed that patients treated with azvudine, especially patients with non-severe COVID-19, had a higher rate of lymphocyte count improvement than controls, indicating the effectiveness of azvudine in the treatment of COVID-19.

In our study, the duration of azvudine treatment varied from 5 to 14 days. Since azvudine was approved on an emergency basis during the COVID-19 pandemic, evidence on its optimal treatment course is limited. The current instructions only recommend the use of azvudine for the treatment of COVID-19 for no more than 14 days. A recent study evaluating the relationship between azvudine treatment duration and efficacy found that azvudine administration for at least 7 days could reduce the rate of 28-day disease progression of COVID-19.[38] In terms of efficacy in outpatients with COVID-19, azvudine treatment has been proven to have good compliance and reduce the rate of COVID-19-related hospitalization.[21,38] Moreover, Yang et al[39] found that azvudine was cost effective in treating outpatients with mild-to-moderate COVID-19.

In terms of safety, we found no significant differences in liver and renal function between the azvudine-treated and control groups. Consistent with our findings, Shang et al[28] found that azvudine therapy for COVID-19 in patients undergoing hemodialysis did not impair liver or renal function. Furthermore, a systematic review showed a reduction in the frequency of adverse events with azvudine treatment compared with placebo or standard treatment.[17] Thus, existing studies suggest that azvudine has a good safety performance.

This study had several limitations. First, although this study used PSM to adjust for major confounders, it was impossible to exclude all confounding factors because of its retrospective design. Second, although we assessed in-hospital mortality, the short follow-up period did not allow us to adequately investigate the effect of azvudine on mortality. Third, this was a single-center study that may have led to a data bias.

Conclusion

In our analysis of patients with COVID-19, azvudine treatment shortened the length of hospital stay and increased the rate of lymphocyte improvement. This effect was more pronounced in patients with non-severe COVID-19. No drug-related liver or kidney function impairments were observed in the patients with COVID-19 that were treated with azvudine. Taken together, our findings support the use of azvudine in patients with non-severe COVID-19.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of Guizhou Provincial People's Hospital (No. [2022] 113). Due to the retrospective design and the use of anonymized data, the requirement for informed consent was waived.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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